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ASEPTIC PLEURITIS EXPERIMENTALLY PRODUCED*

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RENEWED interest in the problem of pleural reaction has been evidenced since the feasibility of lobectomy and pneumonectomy has been shown by many thoracic surgeons. It has been frequently observed at such operations that when adhesions were present in the pleura, there were fewer infections and the risks of the operation were minimized.

The explanation of this phenomenon has never been definitely established by experimental means. Various investigators have studied the effect of introducing different substances into the pleural cavity and have attempted to learn why and by what means protection was afforded to the pleura.

A condensed review of the literature discloses the following problems which have been investigated by others:

1. When saline solutions are injected into the pleural cavity of a rabbit, the fluid is absorbed according to its tonicity or osmotic pressure; for instance, if a hypertonic solution is used, fluid from the circulation enters the pleural cavity, while with hypotonic solutions, the reverse is true. Experiments[1] have shown that, although a great excess of osmotic pressure in the pleural cavity can determine the flow of fluid from the blood into the cavity, fluid will be taken up by the blood if the difference in osmotic pressures between pleural fluid and blood is not excessive.

2. Particulate matter injected into the pleura[2] is taken up by the endothelial cells in situ and transported in endothelial cells rather than as a free agent. It has been shown also that the parietal pleura appears to be more receptive than the

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visceral pleura. Drainage from the parietal pleura is chiefly into the mediastinal lymph nodes, whereas that from the visceral pleura is at the lymph nodes of the hilus. Occasionally transfer of pigment to abdominal lymphatics is noted, but this is not constant or frequent.

3. Negative pressure in the pleural cavity[3, 4] as it becomes greater permits more rapid absorption of fluid into the pleural space from the lung. Thus, if the lung or part of a lung is so impaired that during inspiration it cannot be expanded to meet completely the depressed diaphragm or the changed position of the thoracic walls, there will be a rapid accumulation of pleural exudate due to the creation of this negative pressure. The rapidity of the absorption of fluid is regulated by the depth and rapidity of respiration and by the osmotic pressure.

4. The resistance of the pleura increases with bacterial injury,[5] providing it is not overwhelming. This is true even when infection is due to air-borne bacteria. Repeated infections not only thicken the pleura but also retard absorption.

5. Absorption of particulate matter from the pleural cavity[6] is mainly through the mediastinum and pulmonary ligament. The visceral pleura and parietal pleura contribute slightly to absorption. The lymphatic system appears to be the only one involved in removing the phagocytic cells which have engulfed foreign substances from the mediastinum.

6. Numerous substances injected into the pleural space, and also any inflammatory condition of the lungs, whether tuberculosis, pneumoconiosis, pneumonia, or even malignancies, may be an irritant to the pleura. The resultant pleural reaction may be of a protective nature, i.e., limiting the movements of the lung, etc.

7. It has also been demonstrated[6] that the mediastinum is a protective mechanism absorbing irritating material present, retaining it as though including it in a sponge, and finally fixing it within itself by the production of connective tissue.

8. There is a close relationship between the reaction of the peritoneum and the pleura to particulate matter.[7, 8]

9. Numerous methods have been used to produce definite adhesions in the pleura, all of which depend upon irritation in some form or other.[6, 8-11]

10. Recent work[12] suggests that the differential leucocyte formula in an area of acute inflammation is a function of the hydrogen ion concentration of the pleural exudate. The cytologic pictures of an inflamed area seem to be conditioned by the pH of the exudate surrounding the injured tissue.

11. It has been suggested recently[13] that the injection of beef broth with a pH of 7.45 after pneumothorax is established produces reactions in the pleura which prevent bacteriolytic and cytolytic products that would inhibit new tissue formation.

12. When the mediastinum is thickened artificially, a so-called "mediastinal splint"[14] is developed. This condition prevents mediastinal flutter and also is a barrier to many types of infection during intrathoracic operations.

13. Particulate matter injected into the pleura incites definite reactions in the pleural tissues, such as macrophages, giant cells, and fibroblasts. Some substances bring a response more quickly than others.[6-8, 11, 15, 16]

14. Many authors[5, 7, 8, 12] assert that the pleural reactions may be of a protective nature.

Despite the studies that have been made by various investigators, there are still several unsolved problems concerning the role of the pleura and its mechanism in the protection of the lungs.

Our object was to determine whether we could produce an aseptic pleuritis by a simple method and later to determine to what degree

pleural thickening and adhesions actually prevented infection and also whether operations on the lung were made safer thereby.

We were successful in finding a simple method of introducing the various substances used intrapleurally. Some of the rabbits were later subjected to various thoracic operations to determine whether the preliminary treatment prevented infection and whether the operations could be performed more successfully.

However, a much larger group of animals must be injected intrapleurally and then operated upon at varying intervals to determine the full value of these procedures.

METHODS AND PROTOCOLS

We have used rabbits rather than dogs, because the general anatomy of their pleura and mediastinum in the greater part is similar to that described in man; and, then too, in dogs both pleural cavities communicate, making it difficult to compare the reaction of the one cavity with that of the other.

In view of the fact that the experiments were to be done aseptically, the animals were given special care during operations and postoperatively.

Operative Technique.—The rabbit's hair was clipped while moist, after sterilization of the area with iodine and alcohol; the remaining hair in the field was merely parted with a pair of forceps. The animal was then covered by an operating cloth with a rectangular opening. Scissors were used to make the initial incision, as the skin of a rabbit is too loose to permit the effective use of a knife.

Pneumothorax was done on all animals under local anesthesia (1 per cent novocain), and from 5 to 40 c.c. of air were injected and manometer readings were taken. Thoracoscopic examination was done frequently to have a direct visual picture of any gross reaction within the pleural spaces. The material was injected into the chest cavity through a needle and syringe. Intravenous nembutal supplemented by ether was used before all surgical procedures. All animals were autopsied at the completion of an experiment, at which time the validity of the aseptic precautions was checked by means of direct smear and culture of the involved pleural cavity.

SUBSTANCES USED INTRAPLEURALLY IN THE RABBITS

By poudrage through thoracoscope and cannula:

1. a. Sterile iodized ½ per cent talc, 2 rabbits
   b. Thymol iodide powder, 1 rabbit
   c. Bismuth formic iodide powder, 1 rabbit.

By syringe and needle:

2. 15 grains talc only, in 5 c.c. sterile normal saline, 2 rabbits
3. 30 grains iodized ½ per cent talc in 5 c.c. sterile normal saline, 8 rabbits
4. Bismuth formic iodide powder (10 grains) in saline (5 c.c.), 2 rabbits
5. 10 grains of thymol iodide in 5 c.c. sterile normal saline, 1 rabbit
6. 10 grains of thymol iodide in 5 c.c. sterile cottonseed oil, 4 rabbits
7. 5 c.c. iodized oil (sterile), 3 rabbits
8. 5 c.c. 2½ per cent gomenol in sterile cottonseed oil, 2 rabbits
9. 1 per cent peptone broth, final pH 7.2, 30 c.c., 2 rabbits
10. Sterile normal saline only, 5 c.c., 2 rabbits; 10 c.c., 1 rabbit

The following are the types of chest operations done and the number performed: biopsy of pleura, two; thoracotomy, six; lung ligation, two; ligation of pulmonary artery, one. Among these (operations), several

TABLE I

GROSS PLEURAL REACTIONS

NO. OF RABBITS	MATERIAL INJECTED	PLEURAL THICKENING			FOREIGN MATERIAL PRESENT ON INJECTED SIDE	MEDIASTINAL FIXATION	EVIDENCE OF SOME FORM OF ADHESIONS DUE TO ANY CAUSE	ADHESIONS					
								FUSION			BAND		
		V	P	M				m	l	b	m	l	b
12	Talc in saline or by poudrage A B C D	3	3	5	7	7	10	9	3	3	6	6	2
3*	Bismuth formic iodide in saline or by poudrage	1	3	2	2	0	3	2	1	1	1	3	2
6	Thymol iodide by poudrage or in cottonseed oil or in saline	2	3	4	5	4	6	3	2	2	4	5	6
2	2½% gomenol in cottonseed oil	1	0	0	2	0	2	1	1	0	0	1	1
3	Iodized oil	2	1	1	3	1	2	0	0	0	1	1	6
2	Peptone broth (final pH 7.2)	0	0	0	1	0	1	1	0	0	1	0	0
3	Normal saline	0	1	0	0	0	0	0	0	0	0	0	0

A=Iodized talc in normal saline or by poudrage.
B=Talc only in normal saline.
C=Iodized talc followed by some surgical procedure.
D=Iodized talc in saline plus some other foreign material followed by some surgical procedure.
V=Visceral.
P=Parietal.
M=Mediastinal.
m=Medial.
l=Lateral.
b=Basal.
*One animal in this series also had talc in saline at an earlier date.

TABLE II

MICROSCOPIC PLEURAL REACTIONS

NO. OF RABBITS	MATERIAL INJECTED	FOREIGN MATERIAL IN PLEURAL TISSUE			FOCAL THICKENING			LYMPH CHANNELS				MACROPHAGES			GIANT CELLS			FIBROBLASTS		
								FOREIGN MATERIAL IN	DILATION OF											
		V	P	M	V	P	M		V	P	M	V	P	M	V	P	M	V	P	M
12	A Talc in saline or by poudrage B C D	7	9	6	8	7	6	7 pos. 5 neg.	7	8	6	9	8	4	2	2	3	8	5	6
3*	Bismuth formic iodide in saline or by poudrage	0	1	0	2	2	1	1	0	1	0	2	0	1	1	0	0	1	2	0
6	Thymol iodide by poudrage or in cottonseed oil or in saline	4	4	0	4	5	0	0	1	0	0	3	5	1	0	1	0	2	4	1
2	2½% gomenol in cottonseed oil	2	2	0	2	2	1	0	1	1	1	2	2	0	2	2	0	1	1	0
3	Iodized oil	1	0	2	2	0	2	0	1	0	1	2	0	2	0	1	0	2	0	2
2	Peptone broth (final pH 7.2)	0	0	1	1	0	1	0	0	0	1	0	0	1	0	0	0	0	0	0
3	Normal saline	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0

A=Iodized talc in normal or by poudrage.
B=Talc only in normal saline.
C=Iodized talc followed by some surgical procedure.
D=Iodized talc in saline plus some other foreign material followed by some surgical procedure.
V=Visceral.
P=Parietal.
M=Mediastinal.
*One animal in this series also had talc in saline at an earlier date.

animals had adhesions severed by open thoracotomy. A total of fifty-three pneumothoraces were given this group of rabbits. Thirty-nine rabbits were used, but not all the animals treated are discussed in this paper. Tables I and II show graphically the results obtained by gross and microscopic examination following the introduction of various substances.

We have taken ninety roentgenograms of the rabbits in various positions. It was interesting to note that in taking these films of small animals it was found important to observe the greatest care in positioning the animal and in using the proper roentgenographic technique. In almost all cases the animal was held upright against a specially constructed board. The distance from the tube was usually 30 in., and ranges from 26 to 36 in. were tried. From 50 to 100 milliamperes were used. The exposure time was usually $\frac{1}{10}$ second; a few were taken at $\frac{3}{20}$ second. Photographs of unusual conditions were made and also photomicrographs of the specific reaction of the lung and pleura.

TALC

The talc used was talcum powder (Merck) purified according to U.S.P. IX for medicinal purposes. It consisted almost entirely of hydrous magnesium silicate with occasional small quantities of aluminum silicate, which has been ground into fine particles not small enough to pass through a sieve having 40,000 meshes to the square inch, and further purified by washing with hydrochloric acid.

The commercial talc was prepared weeks before and sterilized in an autoclave. Later, because it was felt that the iodine was volatilized during sterilization, the talc was autoclaved separately and the iodine was dissolved in ether. Under sterile precautions the iodine solution was added to the talc just before using and then it was dried.

In Bethune's[9] experiments talc was introduced into the pleural cavity by a trochar and cannula through which a thoracoscope was inserted. The thoracoscope was removed and a return air powder blower was substituted. We found this method unsatisfactory, because frequently the powder was drawn back from the pleura when the bulb of the blower was relaxed, and also because the varying pleural pressures thus produced may prove detrimental to the subject. It was found that a mixture consisting of 30 grains of sterile talc freshly iodized in 5 to 10 c.c. of normal saline could be made and introduced into the pleura by a syringe and a needle. This was simple and more effective in producing adhesions and thickening of the pleura than any other method.

The modus operandi of this technique was as follows: A pneumothorax was done in the ordinary manner under local anesthesia; 5 c.c. of the above-described talc suspension was then injected. The animal was rotated in all positions, even with the head down, so that the mixture would be evenly distributed over the pleural bases and mediastinum. The air was then withdrawn from the chest cavity in order that the layers of the pleura would be approximated. In some animals more powder and less fluid was used, and vice versa. In no animal of our series did we find an immediate reaction or later embolism. Within a few days there was no evidence of fluid shown by roentgenogram or by thoracoscopy.

The advantage of using talc mixed with saline was that absorption of the saline solution occurred when the particulate matter as such was distributed over the surface of the lung. It was possible to place the talc powder, which excites a

mild reaction, over the entire pleural surfaces, including the mediastinum. The studies of microscopic sections show what type of reaction occurred.

The protocols of typical experiments with talc follow. Two are given in detail:

A. Iodized (½ per cent) talc introduced either by poudrage or in saline:

Rabbit 19.—On April 24, 1939, under manometric control a pneumothorax of 40 c.c. of air was given. Then 30 grains of iodized (½ per cent) talc in 5 c.c. sterile normal saline was injected into the right pleural space.

April 25: The roentgenogram showed pneumothorax present, with a small amount of fluid in the extreme right base. There was a peculiar triangular shadow with an air-containing space in the lower left chest, which usually is evidence of a bulging mediastinum.

Fig. 1.—Rabbit 19. Posterior view of exposed thoracic cage, showing talc deposits and thickening of pleural surfaces on right side.

May 2: Only a small pneumothorax was present, but no fluid was evident on the roentgenogram.

May 23: The animal was sacrificed by air embolism. Smear and culture from the right chest cavity revealed no microorganisms. Dense yellow patches of foreign material were scattered throughout the injected side, particularly in the vis-

ceral pleura. Both here and elsewhere the pleural surfaces were thickened, including the mediastinal area. No adhesions were noted (Fig. 1). Microscopically it was evident that the pleural thickening was largely the result of lymph stasis. In these greatly dilated channels precipitated lymph was mixed with foreign material and macrophages. This, plus the proliferation of cells lining these channels, frequently gave the appearance of large giant cells (Fig. 2). Between these dilated lymph channels slight macrophagic activity was seen, with scattered fine crystals. Fibroblastic proliferation was also minimal. There was no reaction in the underlying parenchyma except for occasional prominent perivascular lymphatic nodules.

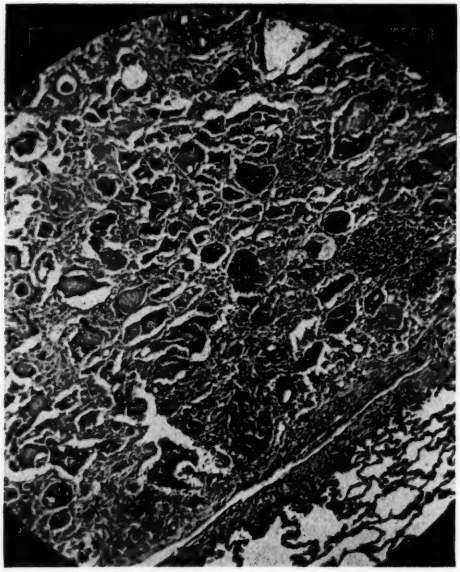

Fig. 2.—Rabbit 19. Talc deposit and resultant reaction overlie and are incorporated with the thickened visceral pleura. Dilated lymph channels containing talc are shown. (×70.)

Comment.—In this rabbit, after one month, gross pleural thickening resulted from lymph stasis and macrophagic activity. No adhesions developed, and microscopically there was very little fibroblastic reaction. One additional rabbit was injected with iodized talc.

Rabbit 34.—On June 1, 1939, 30 grains of iodized ½ per cent talc in 5 c.c. of sterile normal saline were injected into the right pleural cavity. Fourteen days later the animal was found dead. Autopsy revealed foreign material posteriorly and thickening of the mediastinal pleura, together with fusion adhesions. Bandlike adhesions were present laterally and at the base of the lung on the injected side. Microscopically all the pleural surfaces showed zones of focal thickening as well as foreign body crystals. Numerous macrophages were present, some engulfing foreign material. Fibroblasts were present, with the production of connective tissue. Giant cells were not noted. Lymphatic channels were prominent, as were capillaries. Lymph nodes showed hyperemia and occasionally foreign material. An

unexpected finding was the presence of a transverse zone of similar involvement, the appearance of which would be best explained by a needle tract of foreign material in the lung.

Comment.—In fourteen days considerable reaction occurred, including lymph stasis, macrophagic activity, and connective tissue proliferation.

B. Talc only in normal saline solution:

Rabbit 44.—On Aug. 10, 1939, the animal was injected in the right chest cavity with 15 grains of talc *only*, in 10 c.c. of normal saline. Four and one-half weeks later, during an attempted open thoracotomy, the animal died. Foreign material was present at autopsy on both the visceral and mediastinal pleurae, associated with fusion adhesions and partial mediastinal fixation. Numerous band adhesions were also present laterally, but marked pulmonary atelectasis had occurred. Microscopically marked focal thickening and foreign material deposits and macrophagic activity were noted in the visceral and mediastinal pleurae. Similar changes of a moderate degree were present in the parietal pleura. Slight fibroblastic proliferation and early connective tissue were also in evidence. Moderate numbers of dilated capillaries and lymph channels were seen, many of the latter containing foreign crystals.

An unexpected finding was a transverse zone of granulomatous reaction, including foreign material traversing the upper lobe. The appearance of this lesion suggested that of needle tract with injected material.

Comment.—This animal shows well-established, typical gross and microscopic reaction to talc four and one-half weeks after injection. No differences were noted in the reaction to talc alone as compared with that to iodized talc. It was thought that anesthesia contributed to the animal's death. No visceral lesions were noted. One additional animal was used and the same results were found.

C. Injection of iodized talc followed by some operative procedure prior to death:

These procedures were designed to test out the protective value of the talc injections. From a pathologic standpoint, they were segregated into a separate group since some of the tissue changes might have been related to a secondary operative procedure.

Rabbit 15.—On April 14, 1939, under manometric control, pneumothorax of 50 c.c. of air was produced in the right pleural cavity.

April 17: A second pneumothorax of 40 c.c. of air was given.

April 18: The roentgenogram showed good pneumothorax on the right side, with some mediastinal displacement to the left.

April 20: Thirty grains of iodized talc in 5 c.c. of sterile saline was injected into the right pneumothorax pocket. A small thoracoscope was introduced.

The lung was well collapsed.

April 25: The roentgenogram showed the lung expanded. No evidence of fluid was noted.

May 11: The animal was anesthetized by the intravenous injection of 1.5 c.c. of nembutal in the ear. Thoracoscopy was done. Numerous bands of adhesions on the mediastinal side and against the chest wall were seen, and also bands of adhesions at the apex and the interlobar area. The pleural space was dry. Biopsy

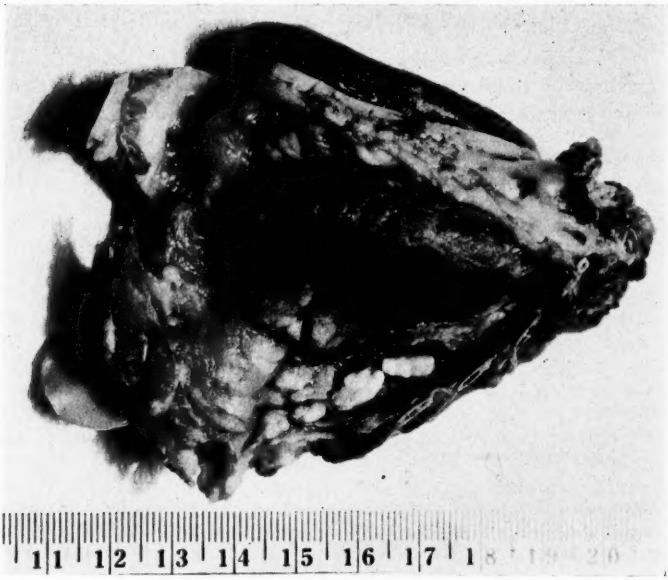

Fig. 3.—Rabbit 15. View of exposed right pleural cavity. The lateral deposits of talc, particularly on the parietal pleura, are well shown. The lung is atelectatic. Note the fusion and band adhesions in the mediastinal area.

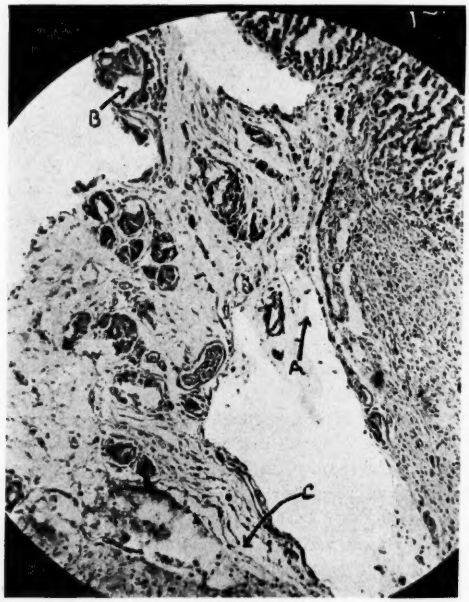

Fig. 4.—Rabbit 15. Low-power view showing: *A*, fixation of lung to thickened mediastinum; *B*, thrombosed lymph channels containing crystals; and *C*, adhesions to diaphragm. (×72.)

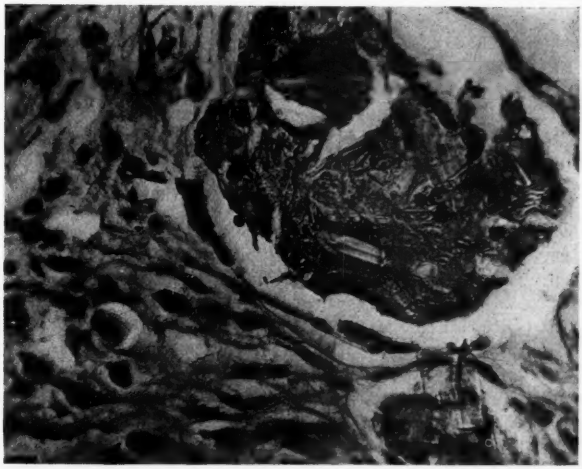

Fig. 5*A*.—Rabbit 15. High-power detail of area marked *B* in Fig. 4. Note collection of crystals in dilated lymph channel. Fewer crystals, macrophages, and fibroblasts are shown nearby. (×430.)

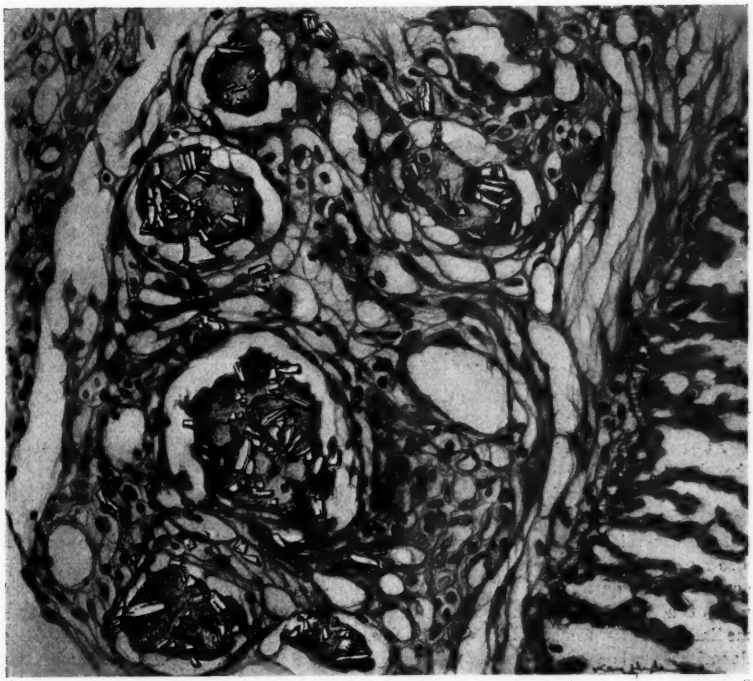

Fig. 5*B*.—Drawing showing widespread distribution of crystals in lymphatic channels. A few crystals are seen in the interstitial tissue.

was taken of the parietal pleura from the costovertebral gutter. There was difficulty with the anesthetic, and the animal died during the procedure.

Autopsy.—Deposits of talc were scattered throughout the pleural surfaces, which were slightly thickened. Adhesions of the lung to the diaphragm and to the mediastinum were noted (Fig. 3). Fusion and also very fine adhesions from the apex of the lung to the chest wall were also present; there were two masses containing talc powder near the pericardium. The right lung was firmly adherent to the mediastinum and marked pulmonary atelectasis was noted. The left lung and pleural membranes were grossly normal. Microscopically slight focal thickenings were present in the visceral pleura. These resulted from fibroblastic proliferation. In addition, macrophages, lymphocytes, and occasional giant cells were present. Foreign material in the form of fine crystals occurred both interstitially within the thickened pleura, and intracellularly within macrophages, giant cells, or dilated lymphatic channels. Many of these lymphatic channels were greatly dilated and contained, in addition, fine lymph thrombi. The parietal pleura showed similar changes. The same process extended from the mediastinal pleura into the adjacent tissue. Connective tissue proliferation in this area was probably responsible for the gross mediastinal fixation noted (Figs. 4 and 5, *A* and *B*). No parenchymal lesions were noted in the lung. Occasionally the perivascular lymphatic tissue appeared prominent, but no foreign material or macrophagic activity was noted. A sternal lymph node was microscopically normal.

Comment.—In this rabbit the gross changes seen at thoracoscopy and at autopsy indicated that pleural reaction to the talc had been established within three weeks. Pathologically the most striking changes were within the mediastinal pleura. Elsewhere they were relatively slight. The biopsy of the parietal pleura gave some index of the nature and extent of the pleural reaction.

D. Iodized talc in saline plus some other foreign material followed by some surgical procedure:

Rabbit 8.—On April 11, 1939, this rabbit received 3 c.c. of iodized ½ per cent talc (old) in sterile physiologic saline in the left pleural cavity, and thirteen weeks later (July 13) a ligation of the left upper lobe hilus was accomplished. At the time of surgery a few soft adhesions were noted. No biopsy of the pleura was done. Two additional procedures has been done in the interval, namely pneumothorax and helium injection after eight weeks (June 8) and lipiodol injection nine weeks later (June 13). On Jan. 30, 1940, nine and one-half months after the talc injections and twenty-three weeks after surgery, the animal was sacrificed. Two hours before death the animal received 50 c.c. of sterile normal saline in the left pleural cavity as part of another experiment.

At autopsy 30 c.c. of fluid was recovered from the left chest cavity (indicating the absorption of 20 c.c. during the two-hour period). The left lung was largely collapsed toward the hilum. A fat pad extending across from the anterior mediastinum occupied most of the apex of the pleural cavity. The parietal pleura was not grossly thickened. Numerous firm adhesions were present about the apex and also medially; here there were fusion and band adhesions, the latter radiating to the costovertebral gutter and to the costosternal arch (Fig. 6). There was also a fine web of adhesions from the mediastinal pleura to the parietal pericardium. The mediastinum was thickened and fixed. Scattered along the mediastinal pleura were deposits of talc. The visceral pleura was thickened at points of attachment of the adhesions. The pulmonary parenchyma showed numerous patches of atelectasis. A fissure was present between the lower lobe and the small surviving remnant of

the upper lobe. The latter measured 2 cm. maximum in diameter and was quite firm on the cut surface. The right pleural cavity was dry, the pleural surface and lungs being grossly normal.

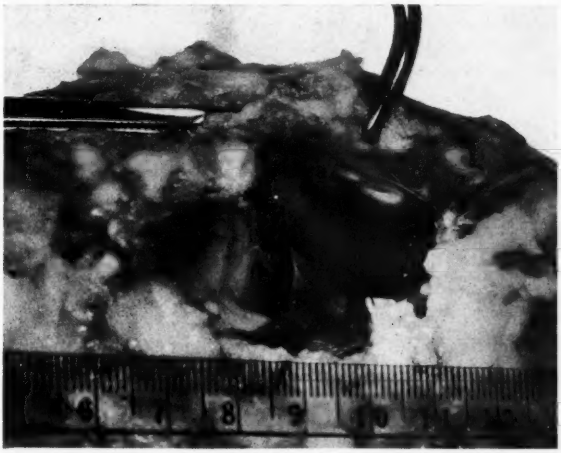

Fig. 6.—Rabbit 8. The lung is deflected downward to show the fine adhesions to the costosternal area. The thickened mediastinum is seen in the background.

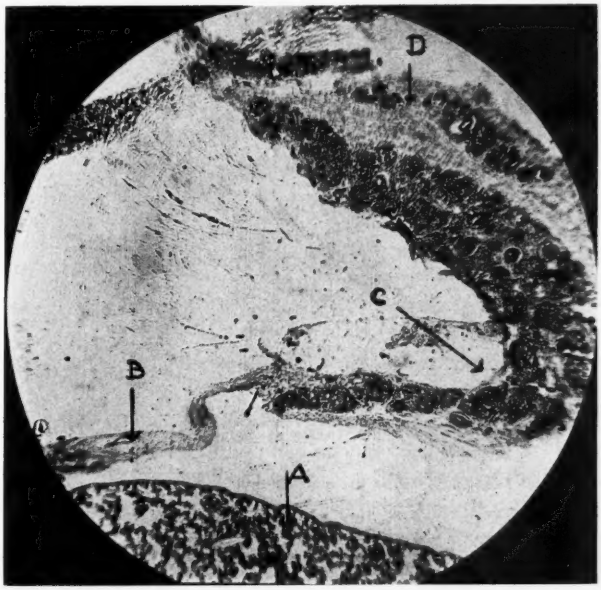

Fig. 7.—Rabbit 8. Portion of lung (*A*) is shown from which thickened visceral pleura is partially detached (*B*). An adhesion containing crystals in the lymphatics (*C*) leads to the thickened parietal pleura (*D*). (Low-power, approximately ×40.)

Microscopic examination of various portions of the pleura showed the most pronounced changes to be in the costophrenic region and about the pulmonary liga-

ment. In this region and elsewhere in the mediastinal pleura, there was diffuse thickening by connective tissue proliferation. Numerous talc crystals were seen, as well as macrophages and lymphocytes. Lymphatic channels were dilated. In the visceral pleura the thickenings were focal and not as pronounced (Fig. 7). The same cellular features were responsible for the change. An occasional dilated lymphatic containing crystals was noted. In the subpleural parenchyma there was noted prominence of the perivascular lymphatics crowded with lymphocytes. No foreign body crystals were seen. The right parietal pleura was normal; two lymph nodes were histologically normal.

Comment.—This rabbit had a ligation of the left upper lobe hilum three months after the injection of the pleural cavity with iodized talc. In the interval two additional procedures had been done, namely, helium pneumothorax and lipiodol injection. At the time of surgery a few soft adhesions were found. When the animal was sacrificed twenty-three weeks later, the pleural reaction to talc was found to be largely mediastinal and not striking. The injected lipiodol and the operative procedures no doubt contributed somewhat to the pleural changes. The animal tolerated the surgical procedures well.

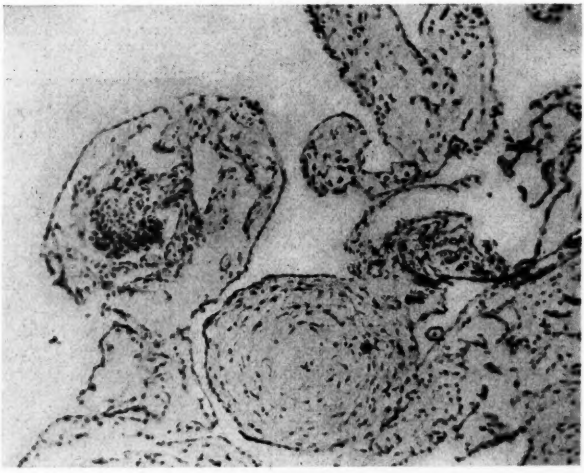

Fig. 8.—Rabbit 6. Biopsy of parietal pleura showing fibroblastic proliferation and macrophagic infiltration. (Low-power, ×100.)

Rabbit 6.—On April 10, 1939, the animal received poudrage (Bethune's method) with old iodized ½ per cent talc. Three weeks later thoracotomy and a biopsy of the parietal pleura were done. This showed fibroblastic proliferation and scattered macrophages (Fig. 8). A few loose adhesions were noted laterally. These broke as the lung collapsed from exposure of the chest cavity. Miliary zones of thickening were also noted at this time in the visceral pleura. Microscopically marked focal thickening was present, associated with fibroblastic proliferation and new connective tissue formation. Less marked macrophagic activity was evident. Dilated lymph channels, some containing crystals, were present.

At the time of the above-described thoracotomy, 1 Gm. of bismuth formic iodide powder was introduced into the pleural cavity. Seven weeks later pulmonary ligation was performed. The animal was sacrificed three months later. At autopsy, marked thickening of the pleural surfaces was noted, as well as fusion adhesions medially and basally about the collapsed lung. A necrotic mass replaced the parenchyma supplied by the ligated pulmonary vessels. The microscopic picture was dominated by an acute inflammatory reaction subsequent to pulmonary necrosis induced by hilar ligation.

Comment.—The biopsy findings three weeks after talc poudrage were characteristic of the expected reaction. The resistance to later surgical procedures may be related to these changes, although the addition of bismuth formic iodide powder complicated the picture.

SUMMARY AND DISCUSSION OF RESULTS WITH TALC

The response of tissues, including the pleura, to talc, along with other silicates, has been studied by several investigators from the standpoint of the potentialities of these substances to induce lesions resembling human pulmonary silicosis.[7, 8, 17-21] In these experiments the various silicates tested, including talc when used, were further ground to a particle size of under 5 micra. The varying results with different substances and with the same substance by different authors indicate that the silicates may produce similar but generally less marked reactions than silica. Miller and Sayers,[7] followed by McCord and co-workers,[21] have developed a standardized procedure for testing the effects of various dusts, using intraperitoneal injection, and have classified them according to the type of reaction produced. With silica and, to a much less extent, with silicates, the tissue reaction is termed proliferative and described as consisting of nodules of connective tissue formed by intensive fibroblastic proliferation. Macrophages are numerous in the early stages and giant cells are rarely seen. Adhesions develop between such nodules. This reaction persists indefinitely and is analogous to the pulmonary lesion of human silicosis.

Not only are the silicates less likely to produce such a lesion, even when ground into very fine particles, as in the above-mentioned experiments, but when used in the large particle size, as in the experiments herein reported, the tissue reaction is less marked and of a different nature. Essentially, it appears to be a foreign body reaction, conditioned more by the mechanical irritation of the injected crystals and less by their chemical nature. Relatively few studies have been made of the tissue reaction to coarse talc thus used. Bethune[9] powdered the pleural cavities of two cats and one dog and noted that in three weeks, six weeks, and two months, respectively, there occurred nodular thickenings of the pleural surfaces comprised of talc crystals, fibroblasts, macrophages, and other cells. These nodules were within the pleura, often within the deeper layers, and resulted, in his opinion, from focal accumulations of talc in transit along pleural lymphatics. In addition,

less marked but diffuse thickening occurred in the pleura between nodules. This thickening resulted from fibroblastic proliferation, with the formation of connective tissue, which in some areas also bridged the pleural cavity, thus constituting adhesions. The tracheobronchial lymph nodes were examined microscopically in one of the animals and found to be normal.

Fienberg,[19] after noting and describing a foreign-body, granulomatous reaction to talc in the skeletal tissue and peritoneum in five human subjects (which he attributed to talc on gloves), proceeded to inject 10 per cent sterile suspension (in distilled water) of talc intraperitoneally into three adult mice. When they were sacrificed at the end of seven weeks, nodules up to 0.3 cm. in diameter were found in the subcutaneous tissue and in the peritoneal cavity. Microscopically these nodules consisted of talc crystals surrounded by macrophages, leucocytes, giant cells, and proliferating fibroblasts. The lesion produced was similar but less advanced than that which had resulted in the human tissues.

Thompson[20] has recently reported the production of firm intrapericardial adhesions within one week after the injection of talc.

In our experiments young adult rabbits were used throughout. The technique and material employed was similar to that described by Bethune, with slight modifications. Slight pneumothorax preceded the introduction of the talc, in order to insure confinement of the foreign material to the pleural cavity. Sterile technique was observed in order to avoid altering the pathologic picture by bacterial contamination. This was further established by direct smears and bacteriologic cultures at autopsy.

From the summary of the findings in Groups A and B, it appears that our results with rabbits are similar to those that have been described above as obtained in the cat, dog, and mouse. Within two weeks the serous membrane lining of the pleural cavity has responded to the injected crystals with a tissue reaction consisting largely of macrophages and foreign body giant cells of the aggregate type. Less numerous plasma cells, lymphocytes, and other leucocytes have also participated. These cellular elements were found both external to the mesothelial lining and within the pleura itself. The proliferation of fibroblasts within the pleura has resulted in the new formation of collagenous fibers which have served to fuse this exudate with the underlying proliferative tissue reaction, thus achieving an increase in pleural thickness varying from slight to several times normal. The mesothelial lining cells have suffered in this process, disappearing in many areas. In some places the mesothelium has persisted and has occasionally become proliferative, piling up in several layers over the underlying thickened pleura. Dilated lymphatic and vascular channels contribute to the pleural thickening. The former at times contained foreign body crystals.

The presence of what appears to be precipitated lymph in some of these channels, together with the barely demonstrable small quantities of foreign material in the draining lymph nodes, suggests that transport of crystals through these channels may have been prevented by previous blockade with foreign body material. The thickening of the pleural surfaces is slight or diffuse and focally nodular. In areas where gross adhesions developed, microscopic examination shows them to be formed by bridges of newly formed connective tissue, at times lined by mesothelium derived from the adjacent pleural lining. A few capillaries and lymph channels were also seen in some of the adhesions, as well as occasional foreign body crystals with associated cellular reaction.

The mediastinal lymph nodes draining the pleural cavities showed no gross enlargement. Occasionally scattered crystals were detected in the pulp, but no reaction resembling that found in the pleura was provoked. Except for occasional slight thickening by connective tissue and prominence of lymphatic lymph channels in the subpleural parenchyma, particularly along interlobular septa, the pleural membrane served as an effective barrier to the injected material. In Rabbit 44 the parenchymal lesions, from their appearance and location, were thought to be the result of accidental deposition of foreign material at the time of attempted injection of the pleural cavity.

In the rabbit there is no gross or microscopic evidence of extension of the foreign material or of any other type of reaction in the contralateral pleural cavity. The parenchymatous organs show no evidence of toxic damage, and the reticuloendothelial elements of the spleen and liver show no abnormality. This probably indicates that little, if any, foreign material has obtained access to the general circulation.

The effect of intrapleural injections of talc on the reaction to subsequent surgical procedures was studied in Groups C and D. It is evident from the summary of the results obtained that no definite conclusions can be drawn. Further experiments with a larger number of animals are to be done.

BISMUTH FORMIC IODIDE POWDER IN SALINE

Bismuth formic iodide, also known as bismuth oxyiodide, is a mixture of formaldehyde gelatin, thymol iodide, and bismuth subiodide marketed as an antiseptic dusting powder (Merck). It is insoluble in water and is decomposed by acids and alkalies. A sterile saline suspension was used.

Rabbit 23.—On May 1, 1939, the animal received 10 grains of bismuth formic iodide powder in 5 c.c. of sterile physiologic saline in the left chest cavity. The animal was sacrificed approximately thirty-five weeks later by nembutal.

During this period two additional procedures were performed. Fourteen weeks after injection, thoracoscopy revealed a collapsed lung and numerous adhesions. Two weeks thereafter 50 c.c. of normal saline were injected into the left chest cavity as part of another experiment. At autopsy foreign material was present along the parietal pleura which was moderately thickened. The visceral pleura was not thickened. Moderate fusion and band adhesions were present medially; less

marked band adhesions were present basally and laterally. There was marked pulmonary atelectasis, but no other parenchymal lesion. An interesting feature was the presence of firm interlobar adhesions, together with foreign material. The opposite pleural membranes were normal.

Microscopically marked focal thickening was present in the visceral pleura, consisting largely of macrophages, giant cells, and lymphocytes. A less marked similar process was present in the mediastinal pleura. The parietal pleura showed foreign material, with no reaction in the area sectioned. In general, most of the foreign material was contained within numerous giant cells.

Neither fibroblastic proliferation nor lymph channels were conspicuous. The draining lymph nodes showed an occasional crystal with no associated reaction. There was some extension of the foreign body reaction along some of the interlobular sectors.

Comment.—This animal showed gross evidence of reaction to the bismuth formic iodide fourteen weeks after injection. It may, of course, have been present much earlier. The pathologic features of the pleural reactions to this substance are similar to those obtained with talc. One difference noted in this particular animal was the presence of little connective tissue proliferation. It was not considered likely that the procedures done during the interval between the initial injection and death altered the pathologic findings to any degree.

Fig. 9.—Rabbit 24. The lung lies collapsed in the exposed chest cavity. Note the fusion adhesions medially and marked band adhesions on the lateral basal areas of the left chest cavity.

Rabbit 24.—On May 1, 1939, the animal received 10 grains of bismuth formic iodide powder in 5 c.c. of sterile physiologic saline in the left pleural cavity. Fifteen weeks later the animal was sacrificed by air embolism.

At autopsy the mediastinal and parietal pleural surfaces were thickened. Fusion adhesions were present medially, and marked band adhesions were present on the

lateral and basal areas (Fig. 9). Extensive pulmonary atelectasis was also noted. Microscopically, moderate focal thickening was present in the visceral and less marked in the parietal pleura. This thickening was almost entirely due to fibroblastic proliferation. Scattered macrophages and lymphocytes were also seen. (Figs. 10 and 11.)

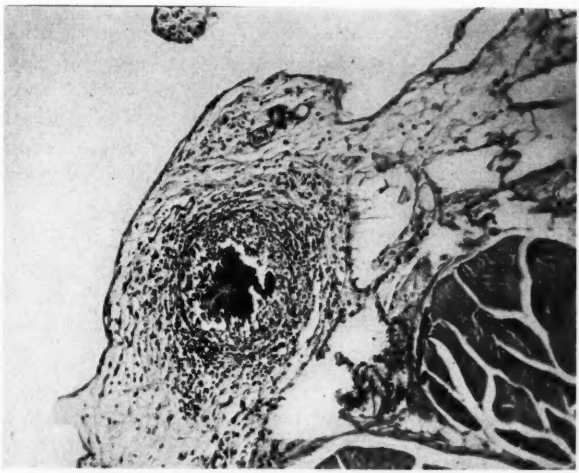

Fig. 10.—Rabbit 24. Granulomatous lesion on parietal pleura surrounding injected foreign material. (×100.)

Fig. 11.—Rabbit 24. An area of focal thickening of the visceral pleura is shown. It consists of newly formed connective tissue infiltrated with macrophages and lymphocytes. Foreign body not shown. (×120.)

Comment.—In this animal the pleural reaction to the injected material consists of gross thickening and adhesions, the result of fibroblastic proliferation. Other cellular changes were not described.

The reaction of the pleura to bismuth formic iodide has not been previously described. Two of our rabbits showed changes attributed entirely to the injection of this powder. These changes consisted of fibroblastic proliferation, with macrophage and lymphocytic reaction

to the foreign material. Lymph stasis was not as prominent a feature as with talc injection. The response of pleural surfaces treated with bismuth formic iodide to secondary surgical procedures has not been studied so far.

THYMOL IODIDE

As with bismuth formic iodide, we have found no descriptions in the literature of the use of thymol iodide in the production of pleural reaction or protection.

Thymol iodide is a mixture of iodine derivatives of thymol, principally dithymol diodide $(C_6H_2CH_3C_3H_7OI)_2$. When dried, it contains not less than 43 per cent iodine. It was injected either by poudrage, in saline suspension, or dissolved in cottonseed oil. Some of the rabbits received additional substances. The following is a summary of the protocols of some of the experiments in this group.

Rabbit 17.—On April 24, 1939, the animal received poudrage (Bethune's method) of thymol iodide into the right pleural cavity. Four weeks later the animal was sacrificed.

Autopsy disclosed large amounts of foreign material, both laterally near the apex and medially at the base of the lung. The parietal pleura was slightly thickened. Marked mediastinal fixation was present, together with moderate fusion and band adhesions. Similar adhesions were present basally and between the lateral pleural surfaces. These adhesions had resulted in firm fixation of the upper lobe at the apex and of the lower lobe laterally and to the diaphragm.

On microscopic examination, focal thickening of the parietal pleura was noted, the result of macrophagic and fibroblastic proliferation, with relatively slight connective tissue formation. Similar changes were not present in the areas of the visceral and mediastinal pleurae examined. There were no changes in the parenchyma; draining lymph nodes were normal, as were the opposite pleural membranes.

Comment.—Approximately one month after the injection of thymol iodide, definite gross changes were present in the form of adhesions, pulmonary fixation, and some pleural thickening. These have resulted from fibroblastic proliferation. Despite the presence of large amounts of foreign material, the histologic alterations were slight.

Rabbit 20.—On April 24, 1939, the animal received 5 grains of thymol iodide in 5 c.c. of sterile normal saline in the left chest cavity. Six weeks later the animal received 5 c.c. of lipiodol by needle in the same cavity. Roentgenograms at this time showed adhesions already present. Ten weeks after the injection of thymol iodide, thoracoscopy revealed a partially collapsed lung from which numerous firm adhesions extended in all directions to the parietal pleura. Eighteen days thereafter (three months after the injection of thymol iodide) a surgical procedure in the form of pulmonary hilar ligation was attempted. During this procedure, numerous basal and lateral adhesions were seen and freed. The mediastinum was accidentally torn during an attempted pulmonary ligation on the left side, and the resultant right pneumothorax, together with a mediastinal hemorrhage, caused the death of the animal.

At autopsy marked thickening of the mediastinal and visceral pleurae was noted, as well as a moderate thickening of the parietal pleura. Marked mediastinal fixation was noted. No grossly enlarged lymph nodes were present. The adhesions across the pleural cavity had been freed surgically. Numerous adhesions were still

present in the interlobar septa. Microscopically there was focal thickening, more marked in the parietal than in the visceral pleura. The thickenings were produced by numerous macrophages together with foreign material. Most of the material was lipoid; some crystals were present. Numerous fibroblasts, together with newly formed connective tissue, were noted. In the parietal pleura many giant cells were present. In the visceral pleura numerous lymphocytes were present, and the lymphatic channels were prominent. Dilated lymphatic channels were also seen in the subpleural parenchyma, particularly along the interlobular septa. Some of these contained crystals. The parenchyma also showed patchy atelectasis. In the regional lymph nodes numerous macrophages, as well as some crystals, were seen in the sinusoids.

Comment.—This animal showed roentgenologic evidence of pleural adhesions six weeks after the initial injection. The adhesions were quite firm when surgery was done four weeks later. Microscopically this was reflected in the increase of fibroblastic proliferation, as compared with the case of Rabbit 26.

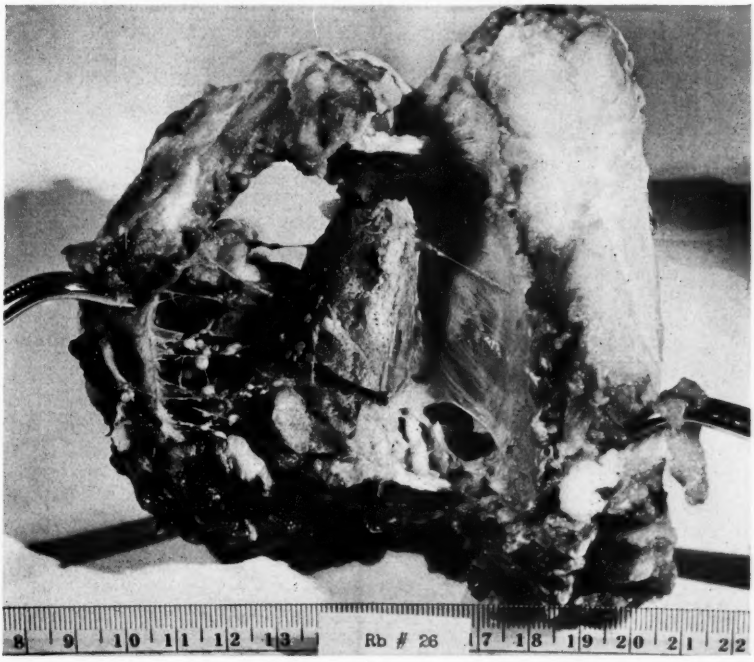

Fig. 12.—Rabbit 26. The atelectatic lung and slightly thickened pleura are well shown. Note the fine intrapleural adhesions on which fatty nodules are frequently strung.

Rabbit 26.—On May 11, 1939, 10 grains of thymol iodide in 5 c.c. of sterile cottonseed oil were injected into the right pleural cavity. Thirteen weeks and six days later the animal was sacrificed by air embolism.

At autopsy considerable foreign material, in many places resembling body fat, was seen in the pleural cavity. Numerous band adhesions were present in many

places between all pleural surfaces. These were soft, flimsy, and unassociated with fusion, fixation, or much thickening (Fig. 12). The lung was partially atelectatic and showed no gross parenchymal lesions. The opposite pleural cavity was grossly normal.

Fig. 13.—Rabbit 26. Thickened visceral pleura. The thymol iodide is largely dissolved in cottonseed oil, producing the vacuoles which are shown. There is slight macrophagic and lymphocytic reaction. (Low-power view, ×100.)

Microscopically, marked focal thickening was present in the visceral and parietal pleurae. Foreign material, numerous macrophages, and a few fibroblasts comprised these zones of thickening (Fig. 13). Many of the macrophages showed phagocytic activity. The material ingested was largely lipoid. A few crystals were also seen. Lymphatics were not remarkable.

No parenchymal lesions were noted in either lung or the abdominal viscera.

Comment.—In this animal large amounts of foreign material were present after thirteen weeks. The crystals have remained dissolved in the oil, which, for the most part, has divided into small globules, grossly resembling body fat. These have evoked little reaction, being largely extracellular and frequently strung like beads on fine band adhesions traversing the pleural cavity. The pleural reaction was relatively slight, and although histologically many of the components of foreign body reaction were present, the gross results did not appear very striking or effective. There was no evidence of toxic damage by the material used.

Rabbit 27.—On May 11, 1939, this animal received 10 grains of thymol iodide in 5 c.c. of sterile cottonseed oil in the right chest cavity. Thirteen weeks and six days later the animal was sacrificed.

At autopsy considerable foreign material was found in the right pleural cavity, and lesser quantities were seen beneath the diaphragm. A slight thickening of the mediastinal parietal pleura was noted, as well as soft adhesions laterally and basally. No fusion or fixation occurred.

Microscopically moderate focal thickening was present in the visceral and parietal pleurae. These thickenings consisted largely of macrophages and lipoid foreign

material with occasional crystals. No fibroblasts or giant cells were noted. Dilated lymph channels were frequently seen, particularly in the parietal pleura about the diaphragm. Similar dilated lymphatics occurred beneath the diaphragm on the peritoneal surface, indicating an avenue for passage of foreign material to the abdominal cavity. Occasional macrophages containing foreign material were seen within these channels. A mediastinal lymph node section showed similar changes.

Comment.—The results obtained were very similar to those in Rabbit 26 which was sacrificed after a like interval. The thymol iodide has remained dissolved in the cottonseed oil and excited relatively slight reaction. Most of the reaction was macrophagic, directed against the lipoid material, and not associated with much fibroblastic response. This was reflected grossly in the absence of fixation or fusion adhesions. In addition, there was evidence of considerable lymphatic absorption of the oil, with likely transfer across the diaphragm.

SUMMARY AND DISCUSSION OF RESULTS WITH THYMOL IODIDE

In the six animals in which thymol iodide was used, either alone or in combination with other substances, some variation in the pathologic changes obtained was seen. When the crystals alone were powdered into the pleural cavity, a thickened pleura with numerous adhesions and mediastinal fixation resulted within four weeks. Histologically, the changes obtained were similar to those yielded by talc poudrage, but not as marked. The attempt to form a saline suspension was not as successful as with talc. When this suspension was used, roentgenographic evidence of adhesions appeared within six weeks, and the gross and microscopic alterations observed at autopsy done fourteen weeks after the initial injection were the same as those described above. Some of the changes may have been due to the additional lipiodol injection. When the thymol iodide was dissolved in cottonseed oil, it made an easy solution with which to work. However, the absorption of thymol iodide seemed to be enhanced, so that the resultant changes were largely those induced by the oil. The gross changes were minimal, with only slight thickening and flimsy adhesions.

The histologic reaction was noted mostly against the oil rather than the dissolved crystals. The failure to develop firm adhesions or considerable fixation was histologically correlated with the diminished numbers of fibroblasts as compared to the reactions of thymol iodide or talc crystals. Another different feature was the presence of giant cells in addition to numerous macrophages. It was interesting and perhaps important to note that in two of the four rabbits in which cottonseed oil was used, foreign material, presumably injected in the pleural cavity, was found at autopsy in the abdominal cavity. If this occurred by transfer through lymphatic channels, further use of this substance would not be advisable.

GOMENOL IN COTTONSEED OIL

Gomenol (niaouli oil) is a volatile, vegetable oil derived from leaves of a species of myrtle tree (*Melaleuca viridiflora* Brong. anogris). It is known to be of low toxicity and to have some bactericidal properties. The chief constituent of the oil (roughly 66 per cent) is cineol. The remainder is made up of a mixture of crystallizable terpineol ($C_{10}H_{18}O$) and its valeric ester. In our experiments, one injection of a 5-c.c. solution of 2½ per cent gomenol in cottonseed oil was employed.

Rabbit 38.—On June 5, 1939, this animal received 5 c.c. of a mixture of 2½ per cent gomenol in 5 c.c. of cottonseed oil in the left chest cavity. Twelve weeks later the animal was sacrificed by nembutal. Autopsy revealed marked pulmonary atelectasis with a few band adhesions to the lateral chest wall and diaphragm, but with no fusion or mediastinal fixation. Large masses of injected material occupied the pleural cavity. Microscopically there was slight focal thickening of the visceral and parietal pleura. These areas showed collections of the injected oil in large vacuoles resembling adult body fat cells. Usually this material was deposited on the pleural membrane; occasionally the mesothelium had extended outward to incorporate some of the lipoid. In these areas, fine capillaries and numerous dilated lymph channels occurred. Lipoid material was not seen in the latter. Numerous macrophages and giant cells contributed to the focal thickening of the pleura. Many contained ingested fatty vacuoles. The reaction of the parietal pleura was similar to that of the visceral, and no reaction was noted in the mediastinal pleura in the area sectioned. Fibroblasts were not a conspicuous feature of the reaction, and connective tissue was not noted. One of the mediastinal lymph nodes, which was grossly normal, showed histologically no cellular reaction. The few finely dispersed vacuoles seen might represent absorbed lipoid material. No lesions were noted in the parenchyma of the lung or in the visceral organs.

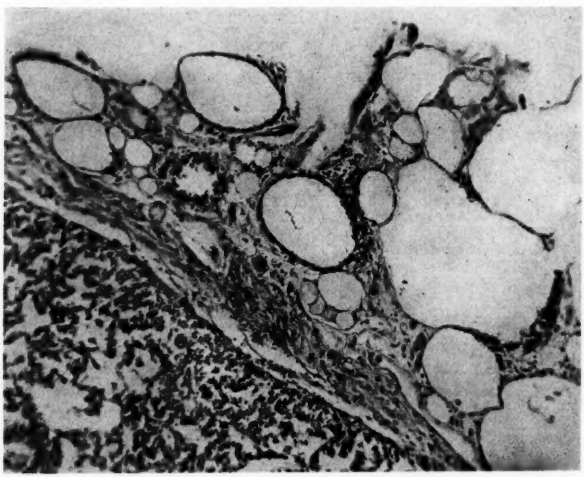

Fig. 14.—Rabbit 37. Low-power view showing gomenol deposits surrounded by slight fibroblastic proliferation, macrophages, and occasional giant cells. (×100.)

Comment.—Twelve weeks after injection this animal showed large amounts of foreign material confined to the pleural cavity. The lipoid

was dispersed in fine vacuoles to which numerous macrophages and giant cells had been attracted. There was little fibroblastic response, and gross adhesions were minimum. Although dilated lymphatic channels were present, they did not show absorption of foreign material nor were thrombi seen.

Rabbit 37.—On June 5, 1939, the animal received 5 c.c. of 2½ per cent gomenol in cottonseed oil. At thoracoscopy six weeks later, numerous adhesions were present, often surrounding gomenol masses. Six weeks thereafter a thoracotomy was done, many of the adhesions were freed, and the animal was then sacrificed.

At autopsy diffuse thickening of the visceral pleura was noted. The lung was atelectatic, and adhesions to the lateral chest wall were present.

Microscopically, the changes in the visceral and parietal pleurae were similar to those described in Rabbit 38. One difference was the presence of scattered fibroblasts (Fig. 14).

SUMMARY AND DISCUSSION OF RESULTS WITH GOMENOL

Gomenol has been employed by several investigators to produce or modify pleural reaction. Saley and co-workers[24] added gomenol in 1 per cent and in 5 per cent solution to cottonseed and paraffin oil. One injection was sufficient to produce the reaction which was the same whether or not gomenol was added to the cottonseed or paraffin oil. Within forty-eight hours after injection of gomenol in cottonseed oil (or of cottonseed oil alone), an acute fibrinous exudate appeared, and soft fibrinous adhesions resulted within one week. After one month these adhesions became firm, coinciding with the development of granulation tissue within the foreign material. Since much of the cottonseed oil appeared to be absorbed, the adhesions were not as persistent as those with gomenol in paraffin oil. These authors felt that gomenol itself did not contribute materially to the pleural reaction. However, Chandler and Gloyne[22] noted the development of soft adhesions twelve days after gomenol alone was injected into the pleural cavity of a rabbit.

In our experiments, one injection of 5 c.c. of a solution of 2½ per cent gomenol in cottonseed oil was employed. The pathologic changes described by previous authors as developing within one month were still present in our experiment three months after injection. Much of the foreign material was still in the pleural cavity, although microscopic amounts had gained access to the regional lymph nodes. Although numerous adhesions developed, they were generally soft and microscopically unassociated with much fibroblastic activity. It is our impression that, in proportion to the amount injected, gomenolized cottonseed oil does not evoke as intensive a reaction as was obtained after a like period with preparations containing talc. Whether the reaction, though not as intense, may be as effective from the standpoint of immunity to secondary surgical procedures will require additional experimentation. The one animal which had open thoracotomy, with freeing of adhesions, withstood the procedure until sacrificed.

IODIZED OIL

We were interested in studying the pleural reaction of iodized oil chiefly from the standpoint of a controlled experiment for those rabbits in which lipiodol was used as an aid in outlining adhesions. We also employed theridol in one rabbit.

Rabbit 39.—On June 8, 1939, the animal received a pneumothorax of 40 c.c. of helium in the right pleural cavity. One week later 5 c.c. of lipiodol (40 per cent) was injected into the same pleural cavity. Two months later more helium was given. The animal was sacrificed twenty weeks and five days after the injection of lipiodol.

At autopsy several masses of injected foreign material were seen between the medial aspect of the middle lobe and the parietal pericardium. The visceral pleura was thickened over the upper lobe. No other thickenings were noted. No adhesions were present. A fibrin body was found in the posterior mediastinum. There were no gross lesions of the opposite pleural cavity or either lung. Microscopically, focal thickening was present in the visceral and mediastinal pleurae. In these areas foreign material consisting largely of fine oil droplets and occasionally a crystal was seen. Cellular reaction consisted largely of macrophages with occasional giant cells, fibroblasts, and newly formed connective tissue. Lymph channels were prominent, and many dilated capillaries also occurred. In addition, in the visceral pleura there were areas of polymorphonuclear leucocytic exudate, and throughout the parenchyma there were many areas of recent bronchial pneumonia. The contralateral pleurae were normal. Mediastinal lymph nodes were normal.

Comment.—In this animal no adhesions were noted twenty-one weeks after the injection of lipiodol. However, considerable histologic reaction of the pleural membranes to the foreign material was present. Two other animals were injected, with similar results. In one of these, theridol was used, and the summary of its protocol follows.

Rabbit 53.—On Nov. 7, 1939, this animal received a helium pneumothorax under manometric control in the right pleural cavity. One week later 5 c.c. of warmed theridol (chlorinized poppy-seed oil, containing 17 per cent iodine [Lilly]) was injected into the right pleural cavity. On Dec. 1, 1939, 5 c.c. of lipiodol was injected. Four days later a thoracoscopy revealed a few fine adhesions, and the animal was then sacrificed.

At autopsy slight focal thickening of the visceral and parietal pleura occurred, together with fine oleaginous fibrinous adhesions mixed with the blood incidental to the recent thoracoscopy. The right lung was collapsed and a small mediastinal hernia was noted.

Microscopically, the reaction consisted of swelling of the mesothelial cells, slight macrophagic and leucocytic infiltration, and the collection of the injected lipoid into large vacuoles. These were at times surrounded by macrophages, scattered fibroblasts, and occasional giant cells.

Comment.—In this animal, which received both theridol and lipiodol, the histologic reaction was greater than with lipiodol alone. Its character was the same, however, and adhesions did not develop.

SUMMARY AND DISCUSSION OF RESULTS WITH IODIZED OIL

Lipiodol is, of course, the oily substance which has been most frequently used as an aid to clinical diagnosis, and, to a lesser extent,

in therapy. According to Binet and Roger,[23] lipiodol is rapidly destroyed and eliminated after absorption into the blood stream, but various tissues differ in their ability to absorb lipiodol and transfer it to the blood stream. In the bronchial tree, where lipiodol is most frequently used, lipophagic activity of the septal macrophages and efficient absorption through the alveolar wall lead to relatively early and effective elimination of the lipiodol. In the subarachnoid space, however, injected lipiodol remains indefinitely. Laplane[23] found that after one year the oil was virtually encapsulated, the only reaction being slight lymphocytic exudation and macrophagic activity. The ability of serous cavities, such as joints, peritoneum, and pleura, to eliminate lipiodol was said to be intermediate between the above-described locations. Lindskog and Tennant[24] have recently reported results with lipiodol injection into the pericardial sacs of cats. The injected lipiodol persisted for at least one year. Some adhesions to the adjacent pleura were produced, but none within the pericardium. Slight macrophagic, giant cell, and fibroblastic proliferation comprised the microscopic reaction about the nodular deposits of injected lipiodol. The reaction of the pleural membranes to the injected lipoid has not been studied very extensively from a pathologic standpoint. Sicard and Forestier[25] abandoned its use after a patient manifested a severe systemic reaction. They made the point that diseased tissues, e.g., inflamed pleura, unlike normal tissues, may have the ability to break down the otherwise perfect and innocuous combination of iodine and poppy-seed oil. The iodine thus released is, in their opinion, the irritating agent. One of us has injected lipiodol repeatedly into the pleural cavities of patients, without noting any clinically untoward reactions. A few experimental observations are on record. Chandler and Gloyne[22] injected three rabbits with lipiodol. Soft adhesions developed within twelve days, formed microscopically from fine granulation tissue. No macrophagic activity was described. An animal sacrificed sixty-four days after injection showed complete absorption of lipiodol, with slight residual pleuritis. They considered the effect of tissue reaction to lipiodol the same as that to gomenol.

Our experiments with lipiodol to date give somewhat different results. No adhesions occurred twenty-one weeks after injection, and only a few soft adhesions developed within nine months. Much of the lipoid material persisted within the pleural cavity throughout the period of observation. A relatively small amount had gained access to the pleural membrane. Histologically, there was evidence of macrophagic activity as well as early connective tissue proliferation. Thus we found that the pleura of normal rabbits reacted but slightly to injected lipiodol and appeared unable to absorb much of it during the period studied. The effect of such intrapleural collections on secondary surgical procedures has not been thoroughly investigated so far. The

changes with theridol were similar to those with lipiodol, but were somewhat better developed in the shorter period of study.

PEPTONE IN BEEF INFUSION BROTH

The pleural reaction to a beef infusion broth containing peptone has recently been described by Rienhoff.[13] In man, within twenty-four hours, Rienhoff noted a fibrinous exudate rich in polymorphonuclear leucocytes. Young granulation tissue developed within the following day, and within one week the exudate within the pleural cavity was largely mononuclear. No adhesions were described. He believed that this pleural reaction was protective against later operative trauma.

We have begun an experimental study of these observations, using 1 per cent peptone infusion broth with a final pH of 7.2. The early reaction of the normal rabbit pleura was not studied. In our thus far limited observations, we have found practically no reaction of the pleura to the injected broth. Some of the other substances employed, such as talc, have shown persistent striking changes at this time interval. So far, we have not attempted secondary surgical procedures on such treated animals.

Rabbit 36.—On June 5, 1939, following preliminary pneumothorax, 30 c.c. of 1 per cent peptone in beef infusion broth (final pH, 7.2) was injected into the right pleural cavity. Five and one-half weeks later the animal was sacrificed. No gross pleural thickening was noted. A small fibrin nodule was seen in the posterior mediastinum about which were a few loose adhesions. Microscopically, in this area the mediastinal pleura was thickened and numerous macrophages and occasional polymorphonuclear leucocytes were mixed with the old fibrin extending toward the mediastinal nodule. The latter contained amorphous, dark-brown material, probably residual from the injected foreign material. Blocks taken elsewhere from the visceral and parietal pleura showed no histologic reaction. The contralateral pleural membranes were also normal.

Comment.—A second animal was used, and in the two rabbits there was very little evidence of reaction due to peptone broth at the time of examination. In one animal, after five weeks a tiny fibrin nodule had formed in the posterior mediastinum, probably about some of the residual injected material. Here there was evidence of slight pleural reaction. After fifteen weeks the only evidence of the injected material or reaction to it was the presence of a small amount of fibrin overlying scattered areas of the visceral pleura.

STERILE NORMAL SALINE

Three animals were injected intrapleurally with sterile physiologic saline and studied at biopsy after five weeks and at autopsy up to thirty weeks after injection; no significant reaction of the pleura occurred.

These served as controls for the experiments with talc and with thymol iodide in saline suspensions.

CONCLUSIONS

Thirty rabbits were injected with various substances intrapleurally, and the gross and microscopic effects are described in detail.

Our experiments have shown that intrapleural injection of talc, thymol iodide, and bismuth formic iodide in saline solutions produces aseptic pleuritis in most instances.

Of these various substances, talc in whatever form administered has seemed to produce the most desirable changes in the simplest fashion. The usual gross features of the pleural reaction to talc were thickening, development of band and fusion adhesions, and mediastinal fixation.

Histologically, the reaction to talc consisted principally in the proliferation of fibroblasts and macrophages, with occasional exudation of other cells. Phagocytosis of foreign material by macrophages, formation of aggregate giant cells containing foreign material, and accumulation of crystals in dilated lymphatic channels contributed to the focal thickening. Adhesions between involved pleural surfaces were formed by connective tissue proliferation, yielding bridges of fine collagen lined with mesothelium.

The reaction to talc, with the large particles used, differs from that which follows use of the more finely dispersed particles of silica or silicates. It is also sharply limited to the pleural cavity (unless injected elsewhere by accident), and regional lymph nodes show slight, if any, change. There is no pathologic evidence of toxic effect from talc injection.

The reaction of the pleura to bismuth formic iodide and thymol iodide was similar to, but not as effective as, that to talc.

Gomenol in cottonseed oil produced soft adhesions which were not as firm as those produced by the injection of talc.

Iodized oil produced a slight reaction in the pleura.

The injection of beef broth, final pH 7.2, in the two animals produced only the slightest pleural reaction in twelve weeks.

Our preliminary observations have yielded some evidence that preliminary treatment of the pleura with various substances used, particularly talc, protects against the hazards of secondary surgical procedures. This problem is under investigation at the present time.

The authors wish to take this opportunity to thank Dr. Herman Zeiler, Chief of the Laboratories of the Cedars of Lebanon Hospital, for his splendid cooperation in placing the facilities of his laboratory at our disposal.

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DISCUSSION

DR. FRANK B. BERRY, New York.—I read and heard Dr. Singer's and Dr. Tragerman's paper with great interest and enjoyment. They and Dr. Jones are to be complimented on this painstaking and convincing experimental work. This is an entirely logical development of the work of a long line of investigators cited by the authors. It is evident from the experiments presented that talc and the other powders used were considerably more efficient in the production of adhesions than were the solutions employed. Clinically, we have used blood, peptone, and gomenol. None of these has proved satisfactory. The only method we have considered effective heretofore has been rubbing both pleural surfaces with gauze, as proposed by Alexander. That is a major procedure in itself and occasionally produces rather sharp reactions.

It would seem from this paper and the earlier publication of Bethune that either direct poudrage or the introduction of talc or an iodide powder in saline into the pleural cavity will produce an adequate aseptic adhesive pleuritis without the risk of the unfavorable reactions that sometimes follow the open operation and rubbing of the pleural surfaces.

This view is also supported by Thompson's recent report on the effect of talc in the pericardium.

I do not know whether or not suspensions of sulfanilamide in saline or direct dusting with the crystals has been attempted by anybody. Experimentally, in the peritoneum a marked reaction is produced. This might produce merely an irritative pleuritis without the adhesive characteristics which are apparently enhanced by the introduction of particulate matter like talc, with the subsequent additional foreign body reaction.

I was extremely interested in the appearance of cottonseed oil in the peritoneum in two of the experiments in which this was used. We frequently see the extension of subdiaphragmatic infections into the pleura, but seldom vice versa. In the last eighteen months, however, we have seen such extension in four instances: (1) a case of lung abscess, empyema, and then anaerobic peritonitis and subphrenic abscess; (2 and 3), two cases of abscess of the lower lobe, with resultant lumbar retroperitoneal and perinephric abscesses; and (4) a case with an obscure supradiaphragmatic focus, probably resulting from a suppurative mediastinal lymphadenitis and then spreading through the diaphragm to present a localized intraperitoneal abscess.

Finally, from the experimental data presented, a definite lymphatic obstruction is produced. Is this a permanent effect, and if so, is it desirable clinically? The latent dangers of a fibrothorax and fibrous mediastinitis are well known, and it would seem to me that a rather cautious attitude should be maintained in advising or employing this method. It will take time, of course, to determine what are the aftereffects of such a permanent obstruction of the lymphatics.

DR. CLARENCE BIRD, Providence, R. I.—Several years ago, after Bethune's publication, in collaboration with Dr. Pat Imes and Dr. Hal Houston of Kentucky, I introduced particulate matter, especially silicon particles, into the pleural cavities of dogs and obtained results quite similar to these which have been shown in rabbits. The adhesions, however, were not broad, dense adhesions covering all lobes, as we had hoped to obtain. They were stringy or patchlike adhesions, and were not sufficiently secure and widespread to fulfill our purpose of a complete obliteration. We found that if we did a phrenicectomy as a preliminary operation, the lower lobes became adherent in more cases. The motion of the lobes evidently had something to do with the failure of adhesions to form. We found also that if the pleural cavity was kept quite dry, more adhesions formed; in general, however, the results were not as satisfactory as we would have wished.

Quite incidentally I would like to say that in our dogs none of the suspension of powder ever ran into the opposite pleural cavity. The lymphatics were always plugged and there was some generalized thickening of the pleural surfaces.

If adhesions could be made broad and permanent, the operation of esophagectomy would be much safer. There is no doubt about it, because the approach is far posterior. Only a portion of the adherent lung would have to be separated and rolled away from the aorta and thoracic spine, and the postoperative care would be much simplified.

DR. CAMERON HAIGHT, Ann Arbor.—Two years ago, through the encouragement of Dr. Jones, we began the use of iodized talc in order to produce adhesions prior to lobectomy. Since then this procedure has been used in most of the patients who have had lobectomy. It has produced satisfactory adhesions, but there is one point I would like to mention particularly; that concerns the amount of talc that one powders upon the upper lobe.

As originally recommended by Bethune, it was stated that the amount of powder should be of about the thickness that a confectioner uses to powder a cake. We have found that when that amount of powder is used, it frequently incites more than the desired amount of pleural reaction, with evidence of pleural fluid, and there is a gravitation of powder down over the lower lobe where it collects in masses such as were illustrated in the slides of Dr. Jones, Dr. Singer, and Dr. Tragerman. We have found that the most desirable result is accomplished when one uses an extremely minimal amount of powder on the upper lobe, in fact much less powder than one would imagine sufficient to do the trick.

I would like to cite one instance in which more than the recommended amount of powder was used. It resulted in a large pleural effusion, and at the subsequent lobectomy the lower lobe was found to be rather densely adherent. Much to our surprise, the upper lobe, which was covered by a thick layer of powder, was not adherent anteriorly because the pleural fluid had prevented approximation of the visceral and parietal pleurae anteriorly early after the poudrage.

In closing, I would merely like to say that the amount of powder we believe sufficient can be described as a very thin film, so thin that one actually can see the pulmonary surface through the powdered pleura.

DR. RALPH ADAMS, Boston.—Hanrahan and I at the Trudeau Foundation in 1938, and Klopstock and I at the Massachusetts General Hospital in 1939, have done a large volume of similar work. The problem of obtaining obliterative sterile pleuritis has intrigued the minds of many men, and a wide variety of methods has been tried. The protection afforded the upper lobe by pre-existing delimiting adhesions in cases requiring lower lobectomy for suppurative disease is very real, and the search for a simple, nonharmful method of consistently providing these adhesions in patients is logical and laudable.

Our work has demonstrated that experimental pleural adhesions can be produced by a variety of physical and chemical agents, and it is agreed that iodized talc is the most satisfactory of the substances depending for their effect upon the action of particulate matter plus chemical irritation. The use of a liquid suspension makes pleural poudrage simpler to perform and easier to control than by the use of atomizers or blowers in conjunction with thoracoscopy. Saline is a satisfactory suspending medium. It has seemed to us that distilled water has the advantage of being itself a temporary tissue irritant and yet readily absorbable. A dilute ether solution also is effective as a suspending medium.

The absorption of particulate matter from the pleural cavity has been studied extensively, and much that was previously known has been confirmed. The lymphatic removal of finely ground material such as carbon or silica is extremely rapid, and intense staining of lymph nodes throughout the mediastinum and both diaphragms has been observed within one-half hour after unilateral injection of India ink. Stiffening of the mediastinum occurs partly from the physical deposition of a mass of foreign material in the mediastinum and diaphragms to the point where further lymphatic absorption is impossible. Larger injections result in the accumulation of inspissated nodules of powder on the pleural surfaces, particularly in the dependent postures. The stiffening also is partially due to the mild inflammatory reaction attendant upon pleural irritation and lymphatic absorption. It is almost impossible by injection methods to obtain pleural thickening or adhesions that are other than fine and stringy in the lateral and superior portions of the chest wall, and they are rarely numerous enough to be of value in limiting infection or maintaining the lung in an expanded state. The amount of fluid formed is surprisingly small. Organization of the small exudate elicited probably accounts for the diffuse bandlike adhesions commonly observed binding the lung to the mediastinal and diaphragmatic pleurae. Serial cauterization of the parietal pleura intercostally provides a fairly

effective method of producing lateral adhesions and avoids the introduction of extraneous material, but probably is painful.

Mediastinal infection following lobectomy possibly is a greater danger than has been realized, but we, fortunately, do not happen to have had an instance in 174 consecutive human lobectomies performed by Churchill, nor in scores of similar animal operations. The mediastinal stiffening undoubtedly is of some mechanical aid, but we have found the rabbit so tolerant of operations on the lung that the use of mediastinal stiffening procedures, or even an intratracheal tube for positive pressure, has been abandoned.

Our impressions at the moment, then, are as follows: We know of no simple or direct method of producing adhesions consistently between healthy pleural surfaces. Methods which work are too often accompanied by pulmonary collapse and are too violent for human use. Postoperative atelectasis depends more often upon intrapulmonary infection than upon the absence of pleural adhesions. The problem of the unexpanded lobe after operation can be solved better by immediate full aeration, closure of the chest with negative pressure, possibly assisted by a positive pressure breathing chamber, and careful application of all measures which will reduce pneumonitis (head down, good drainage, minimum trauma to remaining lobe, pleural cavity drainage).

DR. TRAGERMAN.—There are several points that I should like to make with regard to the comments of the discussants in regard to the talc.

As Dr. Berry and Dr. Bird pointed out, the reaction with talc is essentially supposedly related to silica. There is one important difference, I believe; that is that in silicosis and silicatosis experimentally produced the size of the particle is down in the range of 3 or 4 micra. The commercial talc used here, of course, has a much larger particle, and I think we have to conclude that the effect is largely mechanical and not so much chemical; that is, the amount of chemical damage to macrophages from the silicon particles of this size is no doubt less.

As regards the permanency of the changes, if we can be guided by what has been shown by those who have studied and graded the responses of the peritoneal cavity to injected silicates, these nodules with associated adhesions, as long as they have been studied, are said to be permanent. Whether this constitutes a damage to the organism remains to be seen. We have a number of animals now that have gone at least a year with no visible effects. Whether this foreign material will remain permanently lodged in the pleural lymphatic channels is always problematical. It would seem that eventually there should be slow transportation of the material to the draining lymph nodes. Of course, the parenchyma is protected by the fact that the material injected in the pleural space has no normal access, particularly in the rabbit with thin pleura, to the lymphatic drainage of the lung. The study we did on mediastinal lymph nodes failed to show any, or very much, injected material, and there was little lymphatic reaction.

The use of the material in saline seemed to Dr. Singer to be very desirable because it gave an opportunity to distribute the material widely. It is quite possible that some of these rabbits could be experimented upon with far smaller amounts of material. As a matter of fact, we are beginning to feel that perhaps the adhesions themselves are not so important if one disregards the mechanical benefits of the procedure. For example, as indicated by the studies of Valy Menkin, obstruction of lymphatic channels may be an important factor in the protective aspects of inflammation.

THE ROLE OF EXPERIMENTALLY PRODUCED INTRAPLEURAL ADHESIONS IN EXTRAPLEURAL PNEUMONOLYSIS AND IN THE PREVENTION OF SURGICAL ATELECTASIS IN ANIMALS

EDWARD M. HANRAHAN, M.D., BALTIMORE, MD., AND RALPH ADAMS, M.D., AND ROBERT KLOPSTOCK, M.D., BOSTON, MASS.

TWO problems of thoracic surgery stimulated the present investigation of experimental methods for the production of pleural symphysis.

First, the increasing clinical use of extrapleural pneumothorax in 1938 prompted an attempt at its experimental production in animals. The first operations on dogs anesthetized with nembutal demonstrated that in this animal the absence of a cleavage plane between the parietal pleura and the thoracic wall made the separation of an intact pleura practically impossible. This was equally true of the rabbit and the guinea pig. The cleavage plane of loose areolar tissue, commonly called the endothoracic fascia, which is found in man, is also present in the goat. However, it was desirable that the usual laboratory animals be utilized if possible, and efforts were directed toward finding some means of thickening the pleura of these smaller animals or of creating pleuropneumonic adhesions sufficiently dense to avoid the fatal pneumothorax otherwise invited.

The parietal pleura of the dog, rabbit, and guinea pig is extremely thin. It is tightly adherent to the internal surface of the inner layer of costal periosteum and so closely is it attached to the intercostal muscles that, except over very small areas and under direct vision, it cannot be stripped away. The fact that it could be stripped away at all, however, suggested that if the pleura itself could be thickened or if the intrapleural space could be obliterated by symphysis of the visceral and parietal pleurae, these animals could then be used for extrapleural procedures.

Second, the problem of an unexpanded upper lobe after lower lobectomy for suppurative disease is a very real one. Fortunately, it is an uncommon complication and such atelectasis as occurs usually is transient. There remains the rare case in which persistent atelectasis is attended by distressing sequelae of apical empyema, abscesses, and occasional sequestration curable only by secondary lobectomy and subsequent thoracoplasty, amounting to an almost interminable convales-

From The Edward L. Trudeau Foundation, Trudeau, N. Y., and the Massachusetts General Hospital, Boston.

This investigation was done by Dr. Hanrahan and Dr. Adams during the year beginning Feb. 1, 1938, at Trudeau, N. Y., under a grant from The Edward L. Trudeau Foundation. It was continued during the following year by Dr. Adams and Dr. Klopstock in the Surgical Laboratories of the Massachusetts General Hospital.

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cence. The gravity of the morbidity has stimulated search for a preventive solution. One obvious answer would seem to be pleural symphysis, whereby the upper lobe is prevented from collapsing and the empyema attendant upon lobectomy for suppurative disease, by present methods, is localized to the operative site and easily controlled. Such a situation sometimes has been provided as a result of a preceding infection, but more often the pleural cavity is uninvolved or traversed by scattered adhesions of no infection-limiting or lung-supporting value. Various methods for producing an obliterative pleuritis have been suggested. All are based upon the effect on the pleural surfaces of either mechanical, thermal, chemical, or bacterial irritants. The pleura may be exposed to direct vision and irritated by rubbing with dry gauze, curettage, cutting, or cauterization, and in a variable manner adhesions will follow. Intrapleural injections of various substances may be used without open thoracotomy.

Finally, extrapleural irritants may be used in the form of plombage or intercostal injection for the production of contiguous, intrapleural adhesions.

EXPERIMENTAL PROCEDURES

OPEN THORACOTOMY

The left chests of four rabbits were opened by intercostal incision. In each the left lung was allowed to collapse, and the incisions were closed. Negative pressure was re-established by aspiration of air from the first two animals. The air was allowed to remain in the second two animals. Four weeks later, autopsies were performed. No variation from the normal could be detected in the first two cases. There was partial re-expansion in the second two cases. No alteration in the pleural lining could be seen. These simple preliminary tests were made to establish the fact that simple thoracotomy, with and without aspiration of air, does not cause pleural adhesions.

PLEURAL TRAUMA WITH DRY GAUZE

The left pleural cavities of three rabbits were opened and the parietal pleurae thoroughly traumatized by rubbing with dry gauze. The incision was closed and negative pressure re-established by aspiration of air in each case. Four weeks later, autopsies revealed fine, stringy adhesions irregularly dispersed. There was no fluid, and the lungs showed no evidence of inflammation.

MULTIPLE INTERCOSTAL PLEURAL INCISIONS

The left pleural cavities of six rabbits were opened. Linear incisions were made, dividing only the pleura but exposing the undersurfaces of the intercostal muscles of spaces two to seven, inclusive, from the angles of the ribs to their anterior ends. The incisions were facilitated by the

use of a laryngeal mirror and a small, right-angle knife. The lungs were re-expanded by positive pressure before closure of the incisions into the chest.

One rabbit died after twenty-four hours. The left chest contained 25 c.c. of serosanguineous fluid. There was a marked inflammatory response of the parietal pleura and partial collapse of the left lung.

A second animal was killed seventy-two hours after operation. There was diffuse parietal pleuritis under a heavy layer of fibrin which was applied to the parietal pleura. The lung was not collapsed and there was no visceral pleuritis. A small quantity of serosanguineous fluid lay free in the pleural cavity. One month later, the remaining four animals were killed and examined. Perfect healing had occurred in three, without the presence of adhesions or fluid. Scattered filmy adhesions were present in one, but the chest otherwise looked normal.

PLEURAL CAUTERIZATION

Three rabbits were used. The left chest was opened. A hot cautery of 4-mm. diameter was used for linear traumatization of the pleura overlying intercostal spaces two to seven, inclusive. A third degree burn of the parietal pleura was produced in each intercostal space, extending from the angle to the anterior end of the rib. The chest was closed and all air evacuated. Four days later, one animal was killed. The left pleural cavity was found obliterated by an extremely heavy layer of organizing fibrin densely binding the lung to the chest wall and mediastinum. The lung, however, was partially collapsed. There was no free fluid.

Four weeks after operation, the remaining two animals were killed and similar conditions were found in the two specimens. The heavy layer of fibrin observed in the first animal had been resorbed. The lung remained partially collapsed, the visceral pleura lying approximately 4 mm. from the parietal pleura. Numerous fibrous adhesions extended between the two pleural surfaces and they tended to be grouped along the cauterization lines. The visceral pleura had been touched inadvertently with the cautery in two places in one animal. At these points, actual symphysis to the chest wall had occurred. Microscopic section revealed a diffuse inflammatory reaction, involving the parietal pleura quite extensively and the visceral pleura superficially. There was an area of complete atelectasis almost 1 cm. in diameter surrounding the points of injury to the lung. There was no free fluid.

These results, together with those following multiple intercostal incisions, indicate that injury sufficient to require healing by secondary intention is more favorable to adhesion production than injury which can be cared for by primary intention healing. There is nothing unexpected, of course, in this observation. The influence of pulmonary atelectasis upon adhesions also is suggested. This influence, particularly

in the presence of superimposed lung infection, was observed many times and will be commented upon later.

EXTRAPLEURAL IRRITANTS

Extrapleural irritation in the form of plombage with gauze or gauze soaked in mineral oil is recognized as an effective means of causing localized obliteration of the pleural cavity. A mixture of one part iodine to four parts glycerin was used for the injection of four rabbits.

In Rabbit 1 the chest wall was exposed by reflection of the scapular muscles. Ten injections of 0.1 c.c. each were made between the pleura and intercostal muscles in the fifth and sixth intercostal spaces laterally. Ten days later the animal was killed and examined. There was a violent reaction in the intercostal muscles. Visceral and parietal pleuritis was marked, and numerous thick adhesions bound the two surfaces together locally. Elsewhere, the pleural cavity was free of adhesions but there was a small quantity of serous fluid.

Rabbit 2 received 1 c.c. of the glycerin-iodine solution intrapleurally at the same time that Rabbit 1 was injected. Ten days later it was examined. There was no evidence of the injected solution. There was a mild visceral and parietal pleural reaction without significant collapse of the lung. The pleural cavity contained possibly 10 c.c. of serous fluid. There were no adhesions.

In Rabbit 3 an effort to make an intercostal muscle injection without exposing the chest wall failed, as the material was injected into the muscles of the scapula. A violent inflammatory reaction was observed in these muscles when the animal was examined ten days later.

Rabbit 4 was injected in exactly the same manner as Rabbit 1, using an equal mixture of mineral oil and depolymerized rubber dissolved in the oil. Examination ten days later revealed an intrapleural situation similar to that of Rabbit 1. A deposit of rubber remained as a foreign body in the intercostal muscle.

INTRAPLEURAL TUBERCULIN IN SENSITIZED ANIMALS

Six guinea pigs were injected subcutaneously three times at weekly intervals with 0.25 c.c. of heat-killed tubercle bacilli, strain H 37 (Rv). Three weeks after the first injection the tuberculin skin test was faintly positive and they were given 0.2 c.c. tuberculin (H 37 O.T.) intrapleurally. A moderate pleural effusion resulted which was completely resorbed.

INTRAPLEURAL KILLED CULTURES OF B. COLI

Six guinea pigs received 0.25 c.c. of killed culture of *B. coli* intrapleurally. After one week one pig was killed and showed negligible effects upon examination. Four pigs were again injected with the same amount and one received 1 c.c. This was repeated after another week and the three survivors were killed and examined. In one pig the injected pleural cavity contained thick gelatinoid pus and there was a

smaller deposit of the same material between the lung and the diaphragm in the other pleural space. The pleural surfaces, however, were smooth and shiny.

INTRAPLEURAL KILLED CULTURES OF STAPHYLOCOCCUS AUREUS

Six guinea pigs were injected intrapleurally at weekly intervals with 0.25 c.c., 0.5 c.c., and 1 c.c., respectively. They were examined twenty-five days later and there was no free fluid found in either pleural cavity, although rather diffuse filmy adhesions were evident over both lungs.

PLEURAL INSUFFLATION OF DRY POWDER

Bethune[1] described the production of adhesions following talc "poudrage" of the pleural cavity. An apparatus (Fig. 1), based largely upon his suggestion, was constructed, which embodied certain additional advantages. After filling the sidearm of the glass T tube with powder, the whole apparatus was dry sterilized and was then ready for use. Dogs

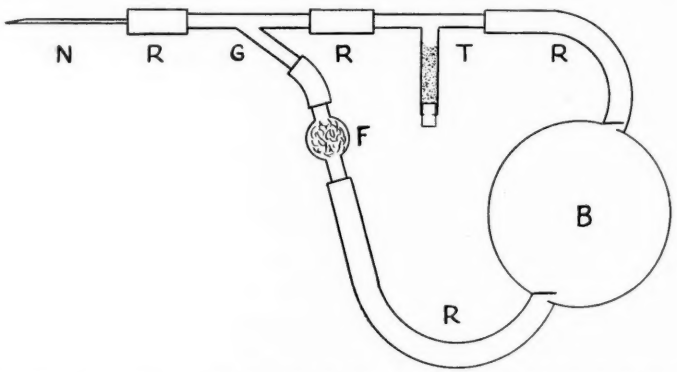

Fig. 1.—Powder blower. *N*, Needle; *R*, rubber tubing connections; *G*, glass connection; *T*, glass tube, powder reservoir which can be rotated to deposit any amount of powder in the straight tube; *F*, cotton filter; *B*, hand bulb with one-way valves.

under nembutal anesthesia were used. About 20 c.c. of air was introduced into the pleural cavity and the needle was connected with the manometer left in place while the larger needle of the powder blower was inserted in an adjacent interspace. After rotating the T tube so that a desired amount of powder was deposited in the crossarm of the T, three or four blasts of the bulb sufficed to pump about 1 Gm. of powder into the pleural cavity, the direction of the needle being changed with each blast. It will be seen from Fig. 1 that the apparatus provided for a closed circuit of air between it and the chest. After the first blast, the bulb was re-expanded by withdrawing from the chest the air introduced by the preceding blast. The amount of pneumothorax was not increased by the procedure, and after the desired amount of powder had been introduced, as much air as

possible was withdrawn from the chest. It had been found by Bethune that better results followed immediate contact of the pleural surfaces.

TALC (HYDROUS MAGNESIUM SILICATE, U.S.P.)

Six dogs were believed to be powdered successfully by this method. One dog was sacrificed immediately afterward and the pleural cavity inspected. There was one rather thick deposit of powder about 4 cm. in diameter on the lung directly opposite the needle. Elsewhere, the powder was evenly distributed over the parietal and visceral pleurae of the upper chest. It was also found less evenly, but abundantly, distributed on the mediastinum and diaphragm. A second dog was probably satisfactorily powdered but was kept for breeding purposes. The remaining dogs were subjected to several powder insufflations at weekly intervals.

After six weeks these four dogs were operated upon under nembutal anesthesia. Four-centimeter lengths of the sixth or seventh rib were removed posteriorly, and through the internal periosteum the lung could be seen moving freely. It was obvious that the talc "poudrage" had failed to bring about obliterative pleuritis and that an extrapleural pleurolysis could not be carried out. Post-mortem examination of these dogs showed small, encapsulated powder deposits on the pleural surfaces, and the adhesions, although frequently present, were very thin and filmy. The diaphragmatic and mediastinal lymphatics were consistently infiltrated and some thickening of the mediastinum had occurred in all cases. Microscopically the encapsulated talc had brought about a pronounced foreign body reaction in which there were numerous giant cells.

Since ordinary talc had failed to produce the desired results in dogs, a mixture of equal parts of metallic iodine and hydrous magnesium silicate (hereafter known as iodized talc) was prepared and inserted into the pleural cavities of rabbits, as follows:

The left chest of Rabbit 1 was opened. Five cubic centimeters of iodized talc was spread by air blast over the upper visceral and parietal pleurae. The wound was closed, all air was aspirated, and negative pressure was re-established. Four weeks later the left chest was reopened. The left lung was found partially inflated but the periphery was collapsed. The visceral pleura was studded with 2-mm. nodules representing collections of powder. No nodules were found on the lateral parietal surface. The lateral pleura was studded with powder nodules, however, on the mediastinal and medial diaphragmatic surfaces. Scattered fine, filmy, and stringy adhesions of no practical value had occurred over the lateral surface of the upper lobe. Thicker, more dense adhesions were found between the surface of the lung and the pleura of the mediastinum and diaphragm. The medial

half of the diaphragm contained a subpleural collection of powder, 0.5 mm. in thickness, lying in situ as a semirigid plaque. The mediastinum, particularly in the anterior half, contained a similar deposit of powder. A mild pleural reaction contributed to the mediastinal and diaphragmatic thickening and stiffening. The right lung and pleural cavity were normal in appearance. Microscopic sections were made from the left lung and pleurae. A superficial inflammatory process involved the visceral pleura and extended for 2 to 3 mm. into the periphery of the lung substance, accompanied by atelectasis. The reaction was accentuated around the nodules of powder. Mediastinal and diaphragmatic distribution suggested complete lymphatic blockage.

Rabbits 2 and 3 were similarly powdered, but died within a few minutes from the shock of the procedure.

Rabbit 4 survived powdering with a mixture of equal parts of metallic iodine, talc, and depolymerized rubber finely ground. This rabbit was killed and examined two weeks later. A situation similar to that in Rabbit 1 was found. Particles of depolymerized rubber remained in the pleural cavity as distinguished from the subpleural accumulations which characterized the more particulate powder.

SILICA DUST (SILEX, 3-MICRA PARTICLES)

The physical properties of this material made insufflation through the powder blower unsatisfactory. It tended to clog the needle and did not spray as a dust nearly as satisfactorily as did talc.

POWDERED CARBON (LAMPBLACK)

Carbon in the form used, even more than silica, tended to adhere to all parts of the powder blower with which it came in contact. Its use demanded such a large needle that, although one blast might expel some material, the apparatus was clogged thenceforth.

INTRAPLEURAL INJECTIONS OF SOLUTIONS AND SUSPENSIONS

GOMENOL IN OLIVE OIL

Six guinea pigs received injections of 1 to 1.5 c.c. of 5 per cent gomenol in olive oil intrapleurally, but only one lived as long as two weeks. The injected right chest showed evident congestion about the periphery of the lung, and in the pleural cavity there was present the remains of a hemorrhagic effusion collected near the pericardium. Both lungs were entirely free in the pleural cavity and there was no free fluid. Tiny droplets of oil were seen. The striking finding was the great enlargement of the mediastinal glands. Two dogs were injected with 10 per cent gomenol in olive oil. One was killed one month afterward and no adhesions were found. The remaining dog was not sacrificed because of intercurrent pregnancy.

IODOCHLOROL

Two cubic centimeters of pure iodochlorol was inserted into the left pleural cavity of a rabbit and the incision was closed after the lung had been completely re-expanded against the chest wall with positive pressure. Eleven days later the left chest was opened and examined. There was superficial inflammation of the lung and of the visceral and parietal pleurae, without adhesions. A small quantity of oil was collected in the cardiophrenic angle. There was moderate enlargement of the mediastinal glands. Significant thickening of the mediastinal or diaphragmatic surfaces had not occurred. Iodochlorol would seem to have only the slightest irritating effect when lying free in the pleural cavity of the rabbit.

GLUCOSE, 50 PER CENT

Five cubic centimeters of 50 per cent glucose solution was injected into the left pleural cavity of a rabbit. Two weeks later examination revealed complete absorption of the solution, without trace of injury.

IODOCHLOROL AND 50 PER CENT GLUCOSE

Two rabbits were used. The left chest was opened under nembutal anesthesia. Two cubic centimeters of equal parts of iodochlorol and 50 per cent glucose was instilled. The lung was completely re-expanded with positive pressure and the incision was closed. Each animal was kept lying on his left side until he awakened from anesthesia. Three weeks later the animals were killed and examined. Each lung surface showed a superficial, diffuse inflammatory process over its whole extent. There was no fluid, and only a few fine filmy adhesions between the lung and the parietal pleural surface had formed laterally. Medially, more numerous, similar adhesions were discovered.

ETHER

Two cubic centimeters of ethyl ether was injected into the left pleural cavity of a rabbit and was followed by immediate death. Examination showed a violent parietal and pleural reaction characterized by edema, great capillary dilatation, and hemorrhagic infiltration of the periphery of the lung.

ETHER AND IODOCHLOROL

Two cubic centimeters of an equal mixture of ethyl ether and iodochlorol was injected into the left pleural cavity of a rabbit, without preceding anesthesia. The animal appeared to become slightly sleepy after one minute but otherwise showed no reaction. Examination ten days later showed a situation identical to that following the use of

iodochlorol alone. Apparently the oil allowed only slow absorption of the ether and prevented permanently injurious effects from its presence.

ETHER AND DEPOLYMERIZED RUBBER

Depolymerized rubber was dissolved in ethyl ether to the point of saturation. Rabbit 1 received an injection of 1 c.c. of the solution into the left pleural cavity. He became sleepy, dyspneic, and unable to stand for a period of three minutes, and then he slowly recovered. The animal died three weeks later. The upper lobe was collapsed but was surrounded by dense adhesions. There was bronchopneumonic consolidation throughout the left lung, but no free or encapsulated fluid on the left. There was a hemorrhagic pleural effusion on the right side.

Rabbit 2 received two injections of 1.5 c.c. of the saturated ether-rubber solution one week apart. Death occurred one minute after the second injection. Examination revealed that extensive adhesions had occurred between the lung and the chest wall. The upper lobe, where the first injection had been made in the hope of causing adhesions over that area, was collapsed and diffusely inflamed, in addition to being adherent to the chest wall. The lower lobe was adherent but did not show gross peripheral evidence of inflammation. Rubber was found throughout the mediastinal lymphatics, in contrast to the absence of rubber within the lymphatics when introduced as finely ground particles coated with talc. The importance of a pulmonary inflammatory reaction in the production of adhesions is demonstrated by the results. The violent reaction produced by ether available for absorption frequently resulted in death. Although it is capable of producing inflammation which will lead to dense adhesions, undesirable pulmonary consolidation probably will be a common feature.

ETHER, IODOCHLOROL, AND DEPOLYMERIZED RUBBER

Ethyl ether was saturated with depolymerized rubber and then mixed with equal parts of iodochlorol. Three rabbits were used.

Rabbit 1 was given 2 c.c. of the mixture in the left chest. One week later 1 c.c. was injected into the pleural cavity through an intercostal space, and two intercostal spaces higher, an additional 1 c.c. was similarly injected. No air was introduced. Two weeks after the second injection the animal was killed and examined. There were thick obliterative adhesions throughout the pleural cavity. The lung was bound to the parietal pleura, mediastinum, and diaphragm. The lung volume was reduced by the thickness of the adhesions. Tiny collections of white oily material (rubber and iodochlorol) were scattered throughout the area. The pleural surfaces were thickened and mildly inflamed. The lung tissue appeared normal.

Two cubic centimeters of the mixture was introduced into the left chest of Rabbit 2, without producing pneumothorax. The animal was

killed and examined seventeen days later. Dense adhesions were found over the posterior half of the upper lobe. There were scattered, thick, fibrous adhesions over the rest of the lung and fibrinous pleuritis over the diaphragm and mediastinum. A moderate inflammatory reaction had occurred in the pleurae, and the periphery of the lung was atelectatic.

Rabbit 3 received 1 c.c. of the mixture through what was believed to be the sixth interspace, and two intercostal spaces higher an additional 1 c.c. was similarly injected. No pneumothorax was produced. One month later the animal was killed and examined. There was a large collection of nodular, grayish material in the anterior costophrenic angle and upward along the mediastinum. There were filmy adhesions over all of the lung and obliterative pleuritis had occurred over the upper third of the lung. In this region also the foreign material had collected in the small globules. There was no fluid and the lung was not collapsed.

MINERAL OIL

Five cubic centimeters of sterile mineral oil was inserted through an open wound into the left pleural cavity of a rabbit. The lung was completely re-expanded with positive pressure and the wound was closed. The animal was killed and examined thirty-four days later. The lung collapsed when the pleura was opened, and there were no adhesions. There was diffuse pleuritis, with thickening in the ventral half of the chest where the injected material had gravitated. The lung was neither collapsed nor inflamed.

MINERAL OIL AND ETHER

Three rabbits were used. Two cubic centimeters of a mixture of 6 c.c. of mineral oil and 2 c.c. of ethyl ether was injected into the left pleural cavity of each rabbit at weekly intervals until a total of three injections had been made in each animal. The first animal died of empyema and pericarditis five days after the last injection. The remaining animals were killed and examined two weeks after the last injection. In each instance, there was widespread, moderate visceral and parietal pleural reaction, with thickening. The lung was partially collapsed. A small fibrinous exudate was organized in some places into easily broken adhesions.

ETHER, MINERAL OIL, AND DEPOLYMERIZED RUBBER

One cubic centimeter of ethyl ether saturated with depolymerized rubber was mixed with 1 c.c. of sterile mineral oil and injected into the left pleural cavity of a rabbit. The animal was killed six weeks later and examined. There was dense diaphragmatic and mediastinal pleuritis, the pleura being 4 mm. thick over the diaphragm. The lung was not collapsed. Laterally, there was no evidence of reaction. The oil

had disappeared, while the rubber was found both free in the pleural cavity and beneath the mediastinal and diaphragmatic pleurae.

The second rabbit received a similar injection. Three days later the left chest was reopened for inspection. There was a mild inflammatory reaction over the entire visceral and parietal pleurae. The lung was not collapsed. There was suggestive pleural thickening along the mediastinum and diaphragm. The rubber solution remained free in the pleural cavity. No adhesions had formed. Seventeen days after the original injection and fourteen days after the inspection, the animal was killed and examined. The upper lobe was partially collapsed, but densely adherent to the chest wall. The rest of the lung was free except for scattered, filmy adhesions, and was completely re-expanded. The lateral inflammatory reaction of the pleura of the lower part of the chest had subsided. The mediastinal and medial diaphragmatic pleurae definitely were thickened. Rubber was found in the ventral parts of the free pleural cavity and also, to some extent, beneath the pleurae of the mediastinum and diaphragm. Probably the rubber found subpleurally reached that location while it was in solution in the ether or mineral oil. As soon as the solvent had been absorbed, further removal of this material by the lymphatics probably became impossible.

A third rabbit received a similar injection. Five days later a second injection of the same material was made one interspace higher. Nineteen days after the first injection a third similar injection was made another interspace higher. Two days later the animal was killed and examined. At least one injection had occurred extrapleurally and lay in the superficial muscles as a confluent mass surrounded by a moderate inflammatory reaction. There was complete, dense, obliterative pleuritis with firm adhesions. The lung was partially collapsed.

SILICA IN WATER

One gram of the silica described above was suspended in 5 c.c. of distilled water. Two guinea pigs were injected with 0.75 c.c. each and examined after two weeks. No changes were noted other than marked lymph gland enlargement. Each of four dogs was injected with 3 c.c. of the suspension. Dog 1 showed no changes referable to the silica. Dog 2 showed on the injected right side moderately dense, but limited rather than diffuse, adhesions over the outer surfaces of the upper and lower lobes. These were separable with more difficulty than the adhesions which followed India ink (to be described). There were filmy apical adhesions. The parietal pleura presented encapsulated nodules of silica about 2 mm. in diameter. The left pleural cavity contained multiple small punctate deposits of the material on the medial third of the diaphragm and on the pericardium and mediastinum. The pleura was thickened only where the silica was deposited and encapsulated.

Dogs 3 and 4 showed no adhesions referable to silica.

A goat was given 5 c.c. of the silica suspension after 5 c.c. of air had been introduced into the pleural space. The pleura was opened and inspected one month later. The lung was free in the pleural cavity and no adhesions were found.

INDIA INK

Rather than a simple suspension of lampblack in water, Higgins India ink, which is such a suspension with the addition of a "glutinous material," as described in *Encyclopedia Britannica,* was used. It was sterilized by boiling for three minutes. One cubic centimeter of India ink was injected into the left pleural spaces of six guinea pigs, without introduction of air. One pig was found dead and examined on the fifth day. The injected pleural cavity was filled with a large quantity of serosanguineous fluid. There were scattered pin-point collections of ink particles, both on and in the visceral and parietal pleurae. There was a remarkable ink injection of the entire plexus of mediastinal and diaphragmatic lymphatics. The opposite chest contained fluid of the same character although less in amount. Ink was seen also beneath the opposite parietal pleura near the hilum. Two pigs were killed and examined on the ninth day. There were a few scattered pin-point nodules under the parietal pleura and a few on the visceral pleura of the injected side. There were a few very fine, filmy adhesions. The mediastinal glands were distended with ink, much more so anteriorly. Beneath the diaphragmatic pleura, in its medial half, was a solid collection of ink. An almost identical picture was seen in the opposite uninjected pleural cavity.

Three pigs received additional injections of 1 c.c. of ink on the fifteenth and twenty-first days. Two animals died within twenty-four hours of these injections. The autopsy findings in the two animals were almost identical. Each pleural cavity contained cloudy, dark fluid which completely collapsed the lung. Ink was collected profusely beneath the parietal pleura which was thickened. There was much ink in the mediastinum and in the medial portion of the diaphragm. One month after the first of the three injections, the remaining pig was killed. On the injected side, the parietal pleura was at least 1 mm. thick and was stripped away from the chest wall without difficulty, leaving the lung covered by a thick, gray layer. Opening this layer revealed between it and the collapsed lung a smooth-walled space containing between 2 and 3 c.c. of reddish-brown, slightly turbid fluid. The visceral pleura also was thickened. There was no fluid in the other pleural cavity and the lung appeared normal. Ink particles were seen beneath the parietal pleura, and the entire surface of the diaphragm was injected. The mediastinum, in which no defect was found, was thickened.

Three dogs received intrapleural injections of between 5 and 10 c.c. of ink, depending upon the size of the dog. Ten weeks later the dogs were sacrificed. Ink had collected in the mediastinal glands beneath the medial portion of the diaphragm and in foci beneath the medial parietal pleura in each instance. All lymphatics on the surface of the lung were sharply outlined. Adhesions were present in all dogs in both pleural cavities. These adhesions were diffuse and dense in two dogs, while in the third they were less dense and easily separated by finger pressure.

A goat received 10 c.c. of India ink after 10 c.c. of air had been introduced intrapleurally. One week later a second injection of 8 c.c. of each was made. Five weeks after the first injection the animal was killed and examined. A rib was first resected near the area of ink injection. The enucleation was remarkably easy as compared with that in the human being. The inner periosteum was carefully incised, and a well-defined cleavage plane was found between it and the parietal pleura, which appeared to be thickened. This cleavage plane could everywhere be developed by the finger posteriorly toward the vertebral column and with less facility anteriorly. On opening of the parietal pleura, it was seen to be stained with ink and there were abundant adhesions between it and the visceral pleura. There was no free fluid. These adhesions stretched somewhat on tension but separated only by cutting. Ink was everywhere in the obliterated pleural space. Ink was found diffusely present in the fixed mediastinum and all lymphatic glands were seen to be enlarged and black when the sternum was lifted. The pleura was thin in the opposite (left) thorax, the lung was free, and there was no fluid. The endothoracic fascial cleavage plane could be developed if considerable care was used. There were traces of ink in the second interspace anteriorly. The left diaphragm was heavily stained with ink in its medial third, with a sharp line of demarcation distinguishing this area from the clean peripheral two-thirds. The pericardium was free of ink, internally and externally. Microscopically, the ink was seen to be in tissue and lymphatic spaces and there was only rare evidence of foreign body reaction.

Ten goats were then prepared for operation by two intrapleural injections of 10 c.c. of ink, given a week apart. Two months later these animals were operated upon, and a typical extrapleural pneumonolysis was attempted on the injected side. Drop ether anesthesia was used, as the margin of safety between the anesthetic dose and the lethal dose of nembutal was too slight. A very satisfactory extrapleural operation was carried out in five of these goats. The space could be developed over the entire upper half of the lung, with the exception of the upper mediastinum. The extent of the adhesions as judged by extrapleural inspection was not constant. In some the lung appeared quite freely

movable. In five animals the pleura was torn during its separation. The resultant open pneumothorax was fatal in only one animal. The stability of the mediastinum and the variable amounts of fixation of the exposed lung to the chest wall in the remaining animals sufficed to allow the chest wall to be closed and the pneumothorax aspirated. The five animals in which a successful operation was performed were started on a regular regimen of extrapleural pneumothorax. The smaller goats required about 200 c.c. of air at biweekly intervals to maintain positive pressures of 15 cm. of water; the larger animals required from 500 to 700 c.c. The longest survival after operation was five months.

Post-mortem examination of these animals showed that in every case the extrapleural pneumothorax had been converted by anemic necrosis of the extensively free parietal pleura into combined intra- and extrapleural pneumothorax, and that the mediastinum had been so far deflected toward the opposite side that the contralateral lung had been compressed to a degree incompatible with life.

DISCUSSION

The search for a simple, nonharmful method of consistently producing obliterative pleuritis has been extended through a large volume of material and a considerable range of experimental methods with informative but variable results. The work has demonstrated that experimental pleural adhesions can be produced by a variety of physical and chemical agents. It is suggested that iodized talc and India ink are the most satisfactory of the substances depending for their effect upon the action of particulate matter plus chemical irritation. The use of a liquid suspension makes pleural poudrage simpler to perform and easier to control than is permitted by atomizers or blowers in conjunction with thoracoscopic or manometric control.

Saline is a satisfactory suspending medium, but distilled water would seem to have the advantage of being itself a temporary tissue irritant, yet readily absorbable. Ether is effective as a suspending medium but elicits incompatibly violent reactions unless controlled by dilution or by use of substances, such as oil, which slow its rate of absorption. The effects noted within two months following one or two injections of silica and talc suspension were comparable with those following poudrage in the dry state.

The absorption of particulate matter from the pleural cavity has been studied extensively and much that was previously known has been confirmed. Dry talc poudrage of the pleural surfaces (Bethune) produced adhesions and pleural thickening to only a slight degree and they were localized in extent. Silica poudrage induced marked lymph gland hyperplasia; it is suggested that if done repeatedly, the resulting lymphatic blockage might well bring about delayed absorption by the pleural lymphatics and eventually diffuse localized reaction. Carbon

(lampblack) poudrage was technically unsatisfactory. In general, these substances are more effectively utilized in suspension. The few cubic centimeters of air used to demonstrate the pleural space should not be aspirated after the suspension has been introduced, as its brief presence probably helps to spread the material more widely.

Iodized talc in watery suspension is consistently effective in thickening the mediastinum and the medial portion of the diaphragm, less reliable in the production of medial pleuropneumonic adhesions, and unreliable in the production of lateral adhesions. Marked and readily demonstrated effects followed the use of carbon suspension; commercial India ink (Higgins) was found most suitable for this purpose. India ink is more than a simple suspension of lampblack in water since it contains also a glutinous material. Its effectiveness increases, within the limits of tolerance, by repeated injection at weekly intervals. The results were not uniform, but in general the use of ink was followed by pleural thickening and visceroparietal adhesions. Its staining qualities are of exceptional experimental value. The lymphatic removal of finely ground material such as carbon or silica is extremely rapid, and intense staining of lymph nodes throughout the mediastinum and medial portions of both diaphragmatic surfaces has been observed within one-half hour after unilateral injection of India ink. Stiffening of the mediastinum occurs partly from the physical deposition of a mass of foreign material in the mediastinum and diaphragm to the point where further lymphatic absorption is impossible. Larger injections result in the accumulation of inspissated nodules of powder on the pleural surfaces, particularly in the dependent position.

The stiffening is partially due also to the mild inflammatory reaction attendant upon pleural irritation and lymphatic absorption of irritant material. It is almost impossible by injection methods to obtain pleural thickening or adhesions that are other than fine, filmy, and stringy in the lateral and superior portions of the chest wall, and they are rarely numerous enough to be of value in limiting infection or maintaining the lung in an expanded state. The amount of fluid formed is surprisingly small. Organization of the small exudate elicited probably accounts for the diffuse bandlike adhesions commonly observed binding the lung to the mediastinal and diaphragmatic pleurae.

Methods of direct mechanical trauma sometimes result in obliterative adhesions; at other times they fail completely for reasons that are not clear. Serial cauterization of the parietal pleura intercostally provides the most effective method found of producing lateral adhesions, but pulmonary collapse attends thermal injury of the visceral pleura. In small animals (dogs, rabbits, and guinea pigs) which have a scant endothoracic fascia, pneumolysis cannot be carried out unless the parietal pleura has previously been thickened or unless the parietal and visceral pleural surfaces are diffusely and firmly adherent.

The bacterial and bacterial-allergic irritants used, including killed cultures of *B. coli*, staphylococcus, and tuberculin in vaccinated animals, only exceptionally gave other than negligible results. Oily solutions such as gomenol resulted only in trifling pleural reactions but did produce marked lymph gland hypertrophy.

Although numerous interesting observations were made, no method of stimulating a fibrinous pleural reaction which would eventuate in fibrous proliferation sufficient to allow the production of a stabilized large extrapleural pneumothorax in animals has been found. Experience has shown that the experimental production of limiting, supportive, obliterative pleural adhesions too often is accompanied by the very ill which it is supposed to prevent, that is, collapse and infection of the lung. Although this is a purely experimental rather than clinical report, it seems pertinent to direct attention to the frequent clinical as well as experimental observation that troublesome postoperative atelectasis in the remaining lobe is almost always a sequel to intrapulmonary infection rather than a precursor of it.

It is suggested that the problem of the unexpanded lobe after operation can be solved better by immediate lung aeration and closure of the chest with negative pressure, possibly assisted by a positive pressure breathing chamber and careful attention to details in the use of all measures which will reduce the hazards of pneumonitis. It is further suggested that there is at the present time no simple or direct method of consistently producing adhesions between healthy pleural surfaces and that methods which work are too often accompanied by pulmonary collapse and are too violent for human use. The introduction of foreign bodies into tissues or tissue spaces is rarely accepted by nature with permanent tolerance. The application of direct trauma to the delicate pleural surfaces, whether in the form of dry gauze wiping, multiple intercostal incision, or serial cauterization, violates fundamental principles of gentleness and delicacy and is difficult for the surgical conscience to accept.

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THE TREATMENT OF ESOPHAGEAL VARICES BY INJECTION OF A SCLEROSING SOLUTION

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VARICES of the esophagus are by no means uncommon, and because of the possibility of hemorrhage which accompanies these varices, they are a constant source of danger to the life of the person afflicted with them. That esophageal varices are not an uncommon source of gastrointestinal hemorrhage is apparent from the observations of Rivers and Wilbur, who found in a review of the histories of 668 patients who came to the Mayo Clinic with a primary complaint of hematemesis, that the bleeding was attributable in 5 per cent of the cases to cirrhosis of the liver or splenic anemia. That esophageal varices are of even greater importance in the production of fatal gastrointestinal hemorrhage would seem apparent from the studies of Preble, who in a review of sixty cases in which gastrointestinal bleeding was fatal, found that esophageal varices were present in 80 per cent. Furthermore, in 50 per cent of the patients who had such varices, Preble was able to demonstrate macroscopic evidence of perforation of a varix. McIndoe, in a review of twenty-six cases in which far-advanced cirrhosis of the liver was fatal, found that the cause of death in thirteen cases, or 50 per cent, was gastrointestinal hemorrhage. It becomes readily apparent, therefore, that any procedure which may assist in preventing bleeding from esophageal varices is worthy of the most serious consideration.

The etiological background of the development of esophageal varices is not always clear in each instance of the condition. Although Banti's disease and splenic anemia are the conditions most frequently found to be associated with the development of esophageal varices, they cannot, as Dock and Warthin have pointed out, be regarded as distinct clinical entities, but occur as a result of obstruction of the portal or splenic vein. Many theories have been advanced to account for obstruction of the portal or splenic vein; however, they will not be discussed in this presentation. The physiologic changes involved in the development of esophageal varices have been very well demonstrated in the anatomic studies of McIndoe and of Kegaries[5] (Fig. 1). Obstruction of the veins may be produced by either intrinsic or extrinsic factors. With the development of obstruction of the portal or splenic vein, there is an attempt on the part of nature to establish an anastomosis by means of which the blood from the portal circulation can return to

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the general systemic circulation. This, as a rule, will take place through channels of communication that already exist. The route that is to be selected is somewhat dependent on the site of the obstruction in the splenic or portal vein. According to McIndoe, the communication that will be established between the portal and caval systems usually takes place through one of three sites (Fig. 2): (1) at the point of transition between absorbing and protective epithelium, either between the coronary vein of the stomach and the intercostal, the azygos, and the diaphragmatic veins, or at the superior hemorrhoidal vein with the middle

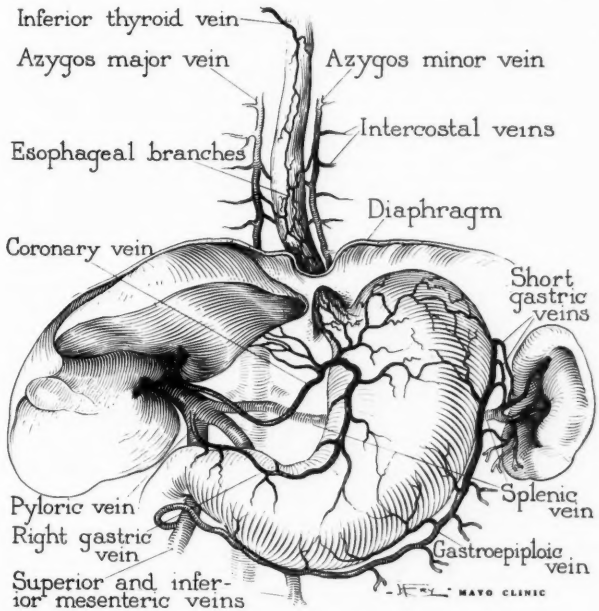

Fig. 1.—Drawing showing the relationship of the coronary vein of the stomach to the esophageal veins.

and inferior hemorrhoidal veins; (2) at the site of embryologic circulation—the falciform ligament containing the paraumbilical veins; or (3) at all situations within the abdomen in which the gastrointestinal tract, its appendages, or glands developed from it become retroperitoneal developmentally or adherent to the abdominal wall pathologically.

The communication that occurs between the coronary vein of the stomach and the azygos, intercostal, and diaphragmatic veins is of the greatest importance, for it is primarily concerned in the development of esophageal varices. Because of their situation, these varices are constantly exposed to trauma, and consequently, are most likely to lead to fatal bleeding. McIndoe has pointed out that in obstruction of the

portal vein the aforementioned communication is the one that is most likely to develop, because it is the most direct and the shortest route between the portal and the general systemic circulation. Furthermore, in the presence of obstruction of the portal vein, the pressure within the portal circulation is increased, and in the absence of valves, the flow of blood through the coronary vein is undoubtedly reversed and

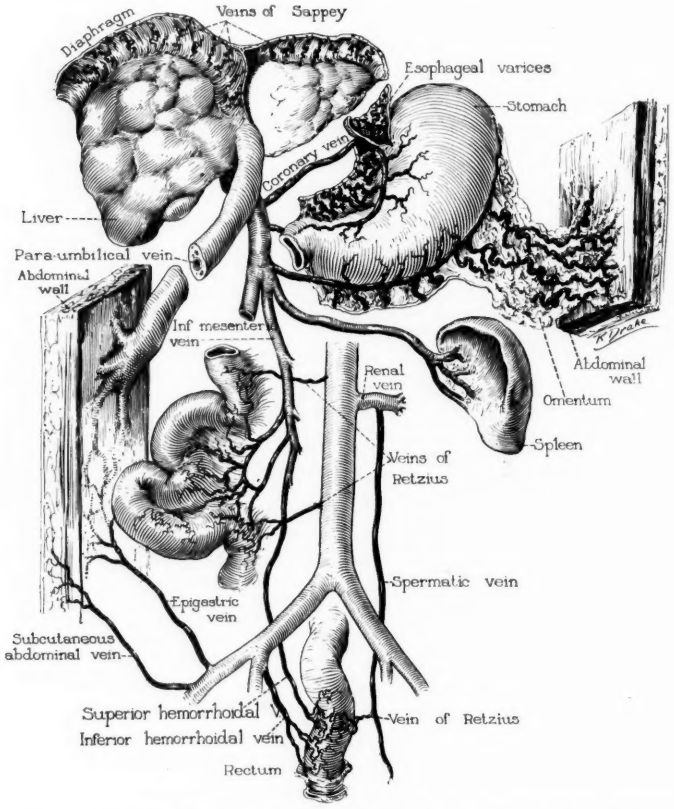

Fig. 2.—Drawing illustrating the most likely source of communication between the portal and systemic circulations.

thus readily exerts pressure on the esophageal plexus. Kegaries[5] has very clearly demonstrated the manner in which anastomosis takes place between the portal and the caval circulation, by way of the cardia and the lower portion of the esophagus. The coronary vein of the stomach branches as it pierces the muscular coats to reach the submucosa of the cardia. In this region, the branches of the coronary vein break up into a number of small longitudinal venules which have no cross communication for a distance of approximately 3 or 4 cm. At this point, they

break up into a rich plexus which anastomoses freely (Fig. 3). The larger trunks are extremely tortuous and run in a longitudinal direction. This plexus of veins communicates by perforating branches with larger periesophageal trunks which likewise run in a longitudinal direction and are usually three or four in number. These latter trunks communicate with the azygos, the intercostal, and the diaphragmatic veins of the systemic circulation. The veins in the submucosa of the

Fig. 3.—Filling of esophageal venules following injection through the coronary vein.

lower part of the esophagus are very poorly supported by loose connective tissue. As a result, varices develop because of the increased flow of blood through the vein and the inability of the muscular and elastic fibers to withstand this increased venous pressure. In addition, there is the effect of the changing suction which takes place in the thoracic cage with respiration. Esophageal varices may involve the greater part of the esophagus, but usually are limited to the lower third portion.

One of the greatest obstacles to the development of efficient procedures for the treatment of esophageal varices has been inability of the

physician to make an early diagnosis of the condition. The first report of esophageal varices that I have been able to find in the literature was that of Power in 1839. For the next eighty-six years very little progress was made in the diagnosis of the condition. Although it was often suspected on the basis of the clinical history, as a rule, if splenomegaly did not exist, it was proved only at necropsy. In 1925, Jackson and his associates called attention to the possible value of esophagoscopy as an aid in the diagnosis of esophageal varices. The procedure did not come into general use, however, because of the fear of producing fatal hemorrhage as a result of abrasion of the varices by instrumentation. If proper care is exercised, however, esophagoscopy can be carried out with a minimum of risk. It was not until 1928 that Wolf first described a roentgenologic technique for the diagnosis of esophageal varices. Kirklin and I, in 1931, called attention to the value of combining roentgenoscopic and esophagoscopic examination as a diagnostic measure, and also pointed out that this combined procedure might also be of value in following the course of developments subsequent to therapy (Fig. 4, *a* and *b*).

Many procedures have been advocated for the prevention and control of bleeding from esophageal varices. Measures such as dietary restrictions, the use of local applications to the varix (diathermy, local compression,[19] and the like), injection of solutions into the general circulation to stimulate coagulation, and venesection, as suggested by Drenckhahn, to decrease the viscosity of the blood have been employed. Such procedures, however, have been merely palliative and therefore of only temporary value.

The surgical procedure that has been employed most frequently is splenectomy. W. J. Mayo pointed out that the procedure should be of value if for no other reason than that removal of the spleen decreases the amount of blood that passes through the portal circulation by approximately 20 per cent. Kegaries[6] has emphasized the fact that in splenectomy, the vessels that run through the vasa brevia and communicate with the esophageal veins are severed, thus eliminating a possible source of communication between the portal and the caval circulation. Many excellent results have been reported in the literature by employment of this procedure. However, it has not entirely solved the problem of gastrointestinal bleeding from esophageal varices. Pemberton and others have advocated omentopexy in addition to splenectomy, with the thought of assisting in establishing anastomosis between the portal and the systemic circulation, thus diverting some of the blood that otherwise would pass through the esophageal varices. In 1929, Rowntree, Walters, and McIndoe,[16, 18] basing their opinion on anatomic studies of the portal circulation, first advocated ligation of the coronary vein as a possible method of preventing bleeding from esophageal varices.

Although this procedure has been of benefit in certain cases, it has not proved to be entirely satisfactory.

Fig. 4.—*a*, Roentgenologic appearance of esophageal varices; *b*, esophagoscopic appearance of esophageal varices.

In 1933, Walters suggested that it might be advisable to inject a sclerosing solution into the varices at the time of ligation of the coronary vein. Dr. Grace has informed me that he has carried out this procedure recently, and that he will describe the method in the discussion of this paper. Pemberton and I became interested in the possibility of injecting a sclerosing solution into the veins directly through an esophagoscope. Before attempting to carry out the procedure in the human being, we thought it would be advisable to perform the operation first in the experimental laboratory. An attempt was made to produce varices of the esophagus in dogs. Much to our chagrin, although we could produce enlarged vessels over the thoracic

wall of the animal, we were unable to produce enlargement of the veins in the esophagus. Consequently, the idea of employing the method in the human being remained very much in abeyance. During 1939, Crafoord and Frenckner of Stockholm reported that they had carried out this form of therapy successfully in the human being, and that the patient had remained symptom-free for approximately three years following treatment. Their report encouraged me to attempt to duplicate the procedure.

REPORT OF A CASE

A man 30 years of age came to the clinic in February, 1940, with a history of recurrent gastrointestinal hemorrhage. A diagnosis of Banti's disease or cirrhosis of the liver had been made elsewhere. The patient apparently had enjoyed the best of health until 1928, in which year he was suddenly stricken with a severe attack of hematemesis. He was hospitalized and repeated administration of transfusions of blood was necessary. The patient recovered from this attack satisfactorily and remained well for approximately one year, at the end of which he suffered a similar attack and transfusions of blood were again required. At this time, enlargement of the spleen was noted and splenectomy was advised. At operation, the spleen, which was approximately nine times normal size, was removed. There is no record of the exact character of the spleen. Following operation, the patient experienced no recurrence of bleeding until 1936, in which year he again began to suffer from hemorrhage. Since that time he had been having recurrent bouts of bleeding which occurred with increasing frequency, and during the year prior to his coming to the clinic, he had had four attacks, the last one occurring in December, 1939.

On physical examination, nothing of unusual consequence was found. The significant observations at laboratory investigation were as follows: There was a reduction in the value for hemoglobin to 9.6 Gm. per 100 c.c., and the blood smear was reported as showing macrocytic, hypochromic anemia of the type seen in cirrhosis of the liver. Roentgenographic examination of the esophagus revealed the presence of esophageal varices involving the lower third portion of the gullet (Fig. 5). It is rather interesting that the test for liver function showed no retention of dye.

A clinical diagnosis of cirrhosis of the liver with associated esophageal varices was made. Dr. Walters, who saw the patient in surgical consultation, suggested that this might be a suitable case in which to attempt control of the bleeding by injection of a sclerosing solution into the varices. Despite the risk involved, the patient was rather anxious to have us attempt the procedure because he lived in constant fear of a fatal hemorrhage.

The patient was subjected to esophagoscopy under local anesthesia, and markedly enlarged varices involving the lower third portion of the esophagus were readily found. They were of such size that they almost completely obstructed the lumen of the gullet. They formed large, bluish, nodular prominences which were soft and compressible. A suitable vein was selected for injection, and, with a 25 caliber needle (Fig. 6), 0.5 c.c. of a 2.5 per cent solution of sodium morrhuate was injected. Much to my surprise, the procedure was accomplished with practically no bleeding. Injections were carried out three more times, at four-day intervals, 1 c.c. of the solution of 2.5 per cent sodium morrhuate being injected on each of these occasions.

The change that took place following the injection treatment was very striking. The vessels that had been injected lost their bluish color and became yellowish-

gray; they were firmer and smaller in size, and the surrounding mucous membrane became less congested. Following the last injection, the lumen of the esophagus, which had been almost completely obstructed by the enlarged varices, returned almost to its normal caliber, and it was possible to look into the stomach without difficulty.

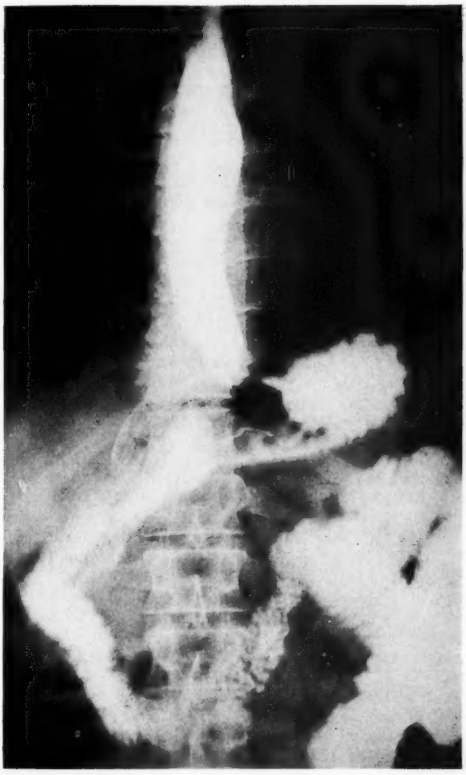

Fig. 5.—Roentgenographic appearance of esophageal varices in the case reported.

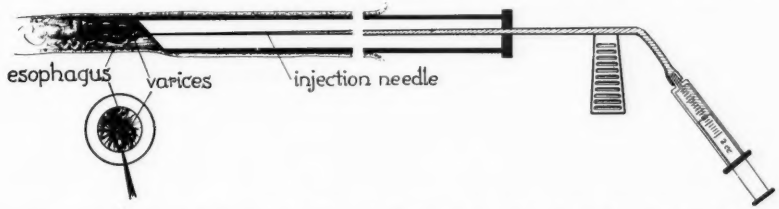

Fig. 6.—Instrument and needle employed in the injection of sclerosing solutions into esophageal varices.

In a recent communication received from the patient, he stated that he has had no further bleeding since his treatment, that his value for hemoglobin has now increased to 81.9 per cent, and that he has been feeling better than he had felt for several years.

CONCLUSIONS

Sufficient time has not elapsed in which to determine the efficacy of the injection type of treatment of esophageal varices, and it may be found necessary to repeat the procedure if further bleeding should take place. It is still uncertain whether the injection should precede or follow splenectomy and ligation of the coronary vein. At the present time, I am inclined to believe that it would be advisable to carry out splenectomy before the injection is attempted. It does seem, however, that this procedure is worthy of serious consideration, inasmuch as it offers a possible method of controlling bleeding that has not responded to any other form of therapy and thus may be successful in prolonging the life of the patient.

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DISCUSSION

DR. EDWIN J. GRACE, Brooklyn.—This paper of Dr. Moersch's which reports satisfactorily controlling esophageal hemorrhage from portal hypertension due to liver damage is an extremely valuable contribution. I feel, in view of the manner in which this hopeless complication of liver damage has been clinically accepted to date, that this report assumes a very important role. Although, with the commendable methods now available for the salvaging of patients with advanced liver damage, this method described by Moersch of controlling so serious a complication is not a palliative, but essentially a curative, procedure.

I have been interested in this type of esophageal hemorrhage and some time ago approached the same problem from a different angle anatomically, and therefore I would like to report a case in which I ligated the coronary vein and injected sodium morrhuate into it.

In October, 1938, a male, aged 53 years, was admitted to the Kings County Hospital suffering from massive esophageal hemorrhage secondary to liver damage. The history showed that this was his fourth hospital admission for apparently the same complaint. At the time of this admission he was markedly exsanguinated, and frequently it was difficult to obtain a blood pressure reading; however, after a few days of supportive therapy, I operated, and after ligation with silk of the coronary vein and the veins of Sappey, 8 c.c. of sodium morrhuate were injected into the coronary vein. This procedure was suggested in 1928 by Walters as a possible method of controlling esophageal hemorrhage.

It is now twenty months since the operation and the patient has not had a hemorrhage since. The hemoglobin has improved from 24 per cent, or 4 Gm., to 80 per cent, or 12 Gm. He is working daily, running an elevator in one of our busy apartment houses. Liver biopsy taken at the time of operation showed considerable liver damage.

His clinical improvement, with the loss of ascites and normal liver function, compels me to feel that this method of approach might supplement the one described by Dr. Moersch.

STANDARDS AND CRITERIA IN ARTIFICIAL PNEUMOTHORAX THERAPY

With a Report of Results

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WHEN a treatment has come into widespread use against a disease, as artificial pneumothorax has in pulmonary tuberculosis, it is well to pause at intervals to look back upon what has been accomplished and to transform the results of a critical analysis into a cautious judgment of its real values. Even if the great value of a treatment cannot be disputed, the enthusiasm over its real virtues easily drowns out critical investigation and patient appraisal. As a result, the number of patients who are really cured by the treatment may be equalized or even exceeded by those who have not improved under it, or who have even been harmed.

In order not to be misunderstood, we state at the beginning that we consider artificial pneumothorax one of the greatest, if not the greatest, advance in phthisiotherapy. It should not impair, but rather enhance, the esteem in which the treatment is held to establish more firmly the basis on which it can be applied and by what criteria its results can be judged. Obviously, in tuberculosis, with its economic and social implications, a compromise between the best available scientific and medical facts and the necessity of public health administration is unavoidable. However, such a compromise can be made safely only if the limits to which large-scale practice may deviate from the highest attainable medical standards are clearly recognized.

It is not the purpose of this paper to discuss in detail the pros and cons of various opinions concerning the indications for air collapse. There is much room for controversy even when, disregarding factors of time and economy, we consider the question on a pathologic basis alone. It may be stated merely that some institutions have used pneumothorax treatment and other forms of collapse therapy in such a large proportion of their patients—one sanatorium has reported over 96 per cent—that they seemingly consider it a universal treatment for pulmonary tuberculosis which can be applied without hesitation and selection in almost any case. This, of course, would dispose of the necessity of discussing the question of indications. However, a critical review of the results of pneumothorax treatment does not bear out the justification of this attitude, as will be shown later in this paper.

Read before the Twenty-Third Annual Meeting of the American Association for Thoracic Surgery (joint meeting with the National Tuberculosis Association) at Cleveland, Ohio, July 6, 7, and 8, 1940.

From the Departments of Medicine and Surgery, University of Chicago.

The recommendation of collapse in noncaseous and nonexcavated tuberculosis of even minimal extent at the earliest possible date is not justified by the observations which can be made on the spontaneous healing of such lesions unaided by collapse. Moreover, while most reports in the literature tend to show that many more lives are saved with the aid of collapse than by mere rest treatment in advanced disease, no such proof can be found with regard to early lesions. The great tendency of the majority of really early tuberculous lesions to heal spontaneously and to do so within a comparatively short time, often without any treatment, seems to have been overlooked in recent years. In this connection it needs to be emphasized that cavernous tuberculosis of any extent cannot be classified as minimal, and that the persistent presence of tubercle bacilli in the sputum, even without roentgenographic evidence of excavation, is a sign at least of beginning cavity formation. This limits the field of minimal tuberculosis considerably. The cavity is the distributor of tuberculous disease to the bearer himself and to others, and is, next to the tubercle, the most important pathologic entity in tuberculosis. In our opinion, only the definite or threatened presence of a cavity indicates collapse therapy. However, not all cavities of any size and roentgenologic appearance offer an absolute indication for air collapse. The transformation of a cavity into a caseous area by retarding or stopping drainage occurs almost as easily as the reverse process of drainage from a caseous area, thus creating excavation. On adequate rest treatment, these filled-up caseous areas frequently remain so permanently, together with disappearance of symptoms and bacilli. If they are small, they may be reabsorbed, or they may calcify either in their entirety or by splitting into a number of very small calceous foci.

The actual size of a fresh cavernous defect cannot be determined from the size of the annular shadow on the initial roentgenogram. The thin-walled cavities of exudative caseous tuberculosis are frequently over-inflated due to the respiratory strain of an active life and quickly become deflated and reduced to the actual size of the defect on complete bed rest. While the original annular shadow may seem to represent a cavity so large that it is judged not amenable to spontaneous healing, the deflated defect can be small enough to heal spontaneously by filling up, confining itself with a wall of fibroid tissue reaction, and eventually calcifying.

We do not wish to imply that all such cavities should be left to the chance of spontaneous healing. Tuberculosis, once known to be excavated, deserves suspicion and observation for many years, even after spontaneous disappearance of the defect from roentgenographic visibility together with seeming clinical recovery. Collapse is frequently indicated after an initial period of observation on bed rest, even though an impressive spontaneous attempt at healing has been observed. The thus defined pathologic basis for a relative indication for collapse leaves the old and

thick-walled residual cavity as the absolute indication which, whether the disease is unilateral or bilateral, demands some form of collapse because the patient cannot be cured without it.

Pneumothorax is definitely contraindicated in the extensive, acute, pneumonic forms of tuberculosis. The patients are gravely ill and untrained in and incapable of proper expectoration of the considerable amounts of sputum which may be produced. The possibility of bronchiogenic distribution, with a dangerous increase of the already great toxic resorption from large areas of quickly caseating involvement, is great, and early collapse tends to hasten that process. It is best initiated when the disease becomes localized and has subsided into the chronic stage, with alleviation of the acute systemic symptoms.

The mass application of pneumothorax treatment in some institutions is regrettable, not only from a practical therapeutic standpoint, but also from an academic point of view. Young physicians receiving training in chest diseases have hardly the opportunity to observe the course of pathologic developments and of the natural healing processes of tuberculosis. Occasionally young visitors to our clinic express astonishment at the spontaneous healing of advanced lesions which can be demonstrated in some of our roentgenograms. We are told that our guests would have initiated collapse therapy immediately in these patients. The spontaneous results are called "exceptional" and "accidental," and yet every experienced tuberculosis physician would agree with us that they are neither miracles nor exceptions but only the abundant manifestations of healing which cannot be followed in the collapsed lung.

The course and success of pneumothorax therapy, pathologically speaking, depends largely upon the reactions of the pleural membranes. It is superfluous to enumerate and demonstrate before this audience the criteria which are affected by the pleural behavior. Barring adhesions, it is the lack of pleural reaction resulting in lability of the mediastinal structures which is likely to impair the possibility of successful collapse to such an extent that surgical collapse appears to be the smaller evil.

It seems that for the application of pneumothorax treatment, one standard ought to be demanded before all others; namely, the combination of collapse with extensive and carefully supervised rest without which no special treatment of tuberculosis can be successful. Especially does the initial period of several months require complete or nearly complete bed rest, regardless of whether or not the patient has had previous rest therapy. The acceptance of this demand should dispose of the practice of purely ambulatory pneumothorax treatment—that is, without even an initial period of institutional care—as insufficient and dangerous. The average patient who is untrained in the general management of his disease and, especially, who has not been made aware of the importance of rest is known to handle himself largely according to the way in which his accustomed mode of living and his economic

status fit best into the newly arrived necessity of office or clinic treatment. Discontinuance of work alone is interpreted as adequate rest, but often even work is not discontinued. The lack of sufficient instruction and education in a busy ambulatorium encourages the patient to look upon his disease as a minor ailment and upon the gas inflations as its sure cure. Reliable information on the results of total ambulatory pneumothorax treatment in this country is not as yet available, but the incidence of complications and failures seems to be considerable and, in their severity, striking.

A young woman was under ambulatory treatment elsewhere when a cavernous tuberculosis with positive sputum developed in the opposite lung. During that period she married, became pregnant, and in the seventh month of her pregnancy was temporarily under our observation in the Chicago Lying-In Hospital. The prognosis of this young woman's disease and of the future of the family, especially that of the unborn child, was unfavorable indeed.

Another patient was recently admitted as an emergency case after ambulatory pneumothorax had been initiated on the previous day, in addition to an air collapse of the opposite lung of long standing. During the night spontaneous pneumothorax had developed on the newly inflated side with nearly fatal results; there would not have been much danger had the patient been under institutional care.

We are well aware that the lack of hospital facilities may dictate a policy of large-scale ambulatory collapse treatment and that this method of closing sources of infection is preferable to not treating cavernous tuberculosis at all. However, it should be looked upon as no more than a makeshift to meet an emergency. Certainly, it would seem exaggerated and even dangerous to hail it as a new and permanent solution to the problem of clinical tuberculosis.

The manner in which the majority of results with artificial pneumothorax treatment have been reported in the literature is largely responsible for an overenthusiasm as to its possibilities in curing tuberculosis, although the number of such reports is small in comparison with the total number of articles which have been published on the subject of air collapse. Out of approximately 2,100 such publications during the decade of 1929 to 1939, only ninety-nine, or 4.7 per cent, could be found which concerned themselves with the results obtained by the treatment.

The basic medical aim of any therapy is to cure disease, that is, to restore the patient permanently and without restriction to the life which he set out to live or lived before he fell ill. A tuberculous patient's return to work does not signify that his tuberculosis is cured. Many authors, especially from abroad, make this "working ability" or "fitness" their exclusive criterion of success; and yet it is common knowledge how long some patients with active tuberculosis can bear full-time work without ever having had treatment of any kind. In

other publications again the emphasis is placed on or exclusive importance is attached to the disappearance of tubercle bacilli from the sputum. This is of considerable epidemiologic importance and a prerequisite for considering excavation as closed, but it is no guarantee for the achieved cure since even untreated cavities can fail to discharge bacilli for periods of months and even years.

The disappearance of symptoms, a gain in weight, and general well-being are easily attained soon after a satisfactory collapse has been established. A distinct line needs to be drawn between what can be considered final results and the initial symptomatic improvement which is so frequent and striking, but is also often misleading as to the ultimate outcome. Many reports of pneumothorax results confine themselves to this phase of the treatment only. Certainly, the term "cure" cannot be applied as long as the lung remains collapsed. The re-expansion is a crucial period, to be watched carefully for the return of manifestations and of activity, and for the roentgenographic reappearance of unhealed involvement. That the disappearance of cavities from roentgenologic visibility may be due to a reduction in size, however considerable, rather than to complete obliteration has already been stated.

No single one of the criteria so far enumerated comes near to assuring permanent success of collapse. Obviously, only the combination of all of them can safeguard to a considerable measure the reliability of pneumothorax results. They can be listed as follows: (1) Restoration of the lung to its physiologic function, i.e., complete re-expansion; (2) adequate roentgenologic evidence of healing of the tuberculous involvement, especially of the disappearance of cavities; (3) return of the patient to normal life, with (4) persistent absence of tubercle bacilli in the sputum, (5) persistent absence of all symptoms of activity, and (6) complete disappearance of all extrapulmonary complications. *Only after at least two years of satisfactory application of these criteria should a patient be considered as cured by the treatment.*

Even then, judged by our own experience and that of others, a minority group of patients will emerge with reactivated and progressive disease after more than two or three years. Tuberculosis does not allow an absolute standard as to its cure, however strict the standard may be. The same criteria, except of course the first one, are applicable to results obtained by surgical collapse methods.

The statistics from eighteen different countries, assembled in Tables I to VI, from as early as 1918, are intended not so much to repeat a presentation of the results with pneumothorax as interpreted by the authors, as to investigate the standards of reporting and thereby obtain more reliable figures on the actual curative value of the treatment. They have been assembled under the headings "Acceptable (or adequate) Standards," "Partially Adequate Standards," "Inadequate Standards," and "Incomplete Information."

TABLE 1

SUMMARY OF TERMINATED CASES OF ARTIFICIAL PNEUMOTHORAX
ACCEPTABLE STANDARDS
MINIMAL OBSERVATION 2 TO 3 YEARS AFTER RE-EXPANSION

YEAR REPORTED	AUTHORS*	COUNTRY	TOTAL NUMBER OF CASES	"CURED" OR "FIT"		DEAD	
				NO.	%	NO.	%
1921	Saugmann	Denmark	172	55	32.0	112	59.3
1921	Miller	Canada	50	17	34.0	17	34.0
1924	Morriss	U. S. A.	49	4	8.2	33	67.3
1927	Rist	France	57	51	89.5	2	3.5
1928	Rist and Hirschberg	France	414	49	11.8	232	56.0
1928	Peters	U. S. A.	167	50	29.9	88	52.7
1930	Amberson	U. S. A.	165	78	47.3	52	31.5
1930	Gravesen	Denmark	134	52	38.8	79	59.0
1932	de Weck and Bachmann	France	51	42	82.4	3	5.9
1932	Packard	U. S. A.	105	62	59.0	24	22.9
1932	Hurrell	England	102	17	16.7	72	70.6
1932	Pai and Gunasagaram	India	104	66	63.5	29	27.9
1932	Bocquet	France	257	74	28.8	60	23.3
1933	Shaw	England	205	130	63.4	62	30.2
1933	Ahlenstiel	Germany	343	125	36.4	138	40.2
1933	Burrell	England	161	44	27.3	110	68.3
1934	Trail	England	80	51	63.8	16	20.0
1934	Rubin	U. S. A.	287	43	15.0	92	32.1
1935	Peters et al.	U. S. A.	347	108	31.1	108	31.1
1935	Dufault and Laroche	U. S. A.	54	35	64.8	9	16.7
1935	Hönich	Germany	100	36	36.0	40	40.0
1935	Morgan and Saley	U. S. A.	107	64	59.8	6	5.6
1935	Miller et al.	Canada	247	83	33.6	96	38.9
1936	Bentley	England	677	173	25.6	406	60.0
1937	Peters	Scotland	112	73	65.2	15	13.4
1937	Harper	U. S. A.	44	17	38.6	3	6.8
1937	Eglee and Jones	U. S. A.	100	93	93.0	1	1.0
1937	Sinding-Larsen	Denmark	158	140	88.6	15	9.5
1937	Rubin	U. S. A.	143	43	30.1	70	49.0
1937	Jeanneret and Famé	Switzerland	144	57	39.6	27	18.8
1938	Aycock and Keller	U. S. A.	200	158	79.0	42	21.0
1938	Douglas et al.	U. S. A.	90	52	57.8	12	13.3
1939	Hjaltested and Törning	Denmark	191	107	56.0	66	34.6
1939	Wambach	Germany	308	109	35.4	161	52.3
Totals (34 reports)		9	5,925	2,358	39.8	2,298	38.8

*The names of the authors are listed alphabetically in the references.

The reports listed under "Acceptable Standards" (Table I) did not necessarily comply fully with the criteria which are suggested in this paper. They include all of those reports in which the details of the material reflected the critical attitude of the investigators, but chiefly those in which the author adhered strictly to the principle of reporting only on patients whose lungs had been re-expanded for a considerable period of time. This was the case in 34 per cent of a total of ninety-nine reports and in approximately 6,000 cases of a total of more than 22,000. A great variation in the mortality figures can be observed in the tabulation. In the main, this is due to some authors reporting only cases of death which occurred after completion of the treatment, while others, recording a high mortality, included all fatalities from the initiation of collapse.

TABLE II

SUMMARY OF "LATE OR PERMANENT RESULTS" OF ARTIFICIAL PNEUMOTHORAX CASES

PARTIALLY ADEQUATE STANDARDS

THIS GROUP CONSISTS LARGELY OF TERMINATED CASES. ALL OF THE PATIENTS HAVE BEEN OBSERVED AT LEAST 4 TO 5 YEARS AFTER START OF PNEUMOTHORAX

YEAR REPORTED	AUTHORS	COUNTRY	TOTAL NUMBER OF CASES	"CURED" OR "FIT"		DEAD	
				NO.	%	NO.	%
1918	Kendall and Alexander	Canada	73	32	43.8	16	21.9
1919	Parfitt and Crombie	Canada	42	11	26.2	24	57.1
1920	Harns	Germany	193	7	3.6	92	47.7
1920	Dorn	Germany	47	15	31.9	25	53.2
1921	Deist	Germany	39	8	20.5	27	60.2
1924	Matson et al.	U. S. A.	480	142	29.6	194	40.4
1924	Maendl	Germany	172	62	36.0	87	50.6
1926	Zinn and Siebert	Germany	183	27	14.8	106	57.9
1926	Schröder	Germany	115	43	37.4	65	56.5
1929	Ćekalov	Russia	154	12	8.0	66	42.7
1930	Arni	Germany	170	36	21.2	124	72.9
1930	Böök	Finland	67	26	38.8	39	58.2
1931	Bălăneseu and Teodoreanu	Rumania	520	206	39.6	111	21.3
1931	Nikolskij and Podzemskaja	Russia	188	20	10.6	23	12.2
1931	Roloff	Germany	262	118	45.0	105	40.1
1931	Šerr	Russia	245	20	8.0	37	15.0
1932	Macfie and Alexander	England	166	45	27.1	72	43.4
1932	Johannsohn and Altschuler	Russia	175	79	45.0	36	20.6
1932	Bernard et al.	France	202	74	36.6	94	46.5
1933	Horster and Federlein	Germany	101	25	24.8	59	58.4
1933	Jessel	England	85	43	50.6	30	35.3
1933	Münchbach	Germany	475	176	37.0	202	42.6
1934	Vinickij	Russia	214	17	7.9	40	18.7
1935	Krasnajanski et al.	Russia	455	73	16.0	82	18.0
1935	Alvarez et al.	Spain	61	14	23.0	7	11.5
1936	Hanna	U. S. A.	76	36	47.4	18	23.7
1937	Tice and Hruby	U. S. A.	1,798	360	20.0	409	22.7
1937	Brand et al.	England	1,359	271	20.0	902	66.4
1938	Schoch	Germany	177	101	57.3	60	33.7
1938	Mondolfo and Molari	Italy	197	94	47.7	72	36.5
1939	Hawkins and Coutts	Canada	134	3	2.2	27	20.1
Totals (31 reports)		10	8,625	2,196	25.5	3,251	37.7

The results reported with partially adequate standards (Table II) differ from those in the previous group only by the omission of the principle to report only patients whose lungs had re-expanded, although a good many such cases were included.

The results grouped under "Inadequate Standards" (Table III) and "Incomplete Information" (Table IV) make up 16.1 per cent and 18.5 per cent, respectively, and together almost 35 per cent of the total number of reports. A much lower mortality was averaged from these tables which explains in part the great optimism derived from such reports. The qualification of standards is summarized in Table V, demonstrating that far less than one-third of all reports have been published with what could be considered acceptable standards. Table VI shows that

TABLE III

OTHER REPORTS OF "LATE RESULTS" OF ARTIFICIAL PNEUMOTHORAX THERAPY

INADEQUATE STANDARDS

YEAR REPORTED	AUTHORS	COUNTRY	TOTAL NUMBER OF CASES	"ARRESTED" OR "CURED"		DEAD	
				NO.	%	NO.	%
1922	Ringer	U. S. A.	85	14	16.5	41	48.2
1929	Elizarov	Russia	70	9	12.7	10	14.3
1930	Sachs	Germany	350	143	40.9	28	8.0
1931	Blaskó	Hungary	147	35	23.8	14	9.5
1931	Herrmann	Germany	125	50	40.0	47	37.6
1931	Rusescu and Gheorghiu	Rumania	126	17	13.5	8	6.3
1932	Lunkevič and Biller	Russia	484	242	50.0	29	7.0
1932	Fuchsmann	Russia	215	46	21.6	13	6.0
1932	Zolotuchin et al.	Russia	426	164	31.0	74	14.0
1933	Grinčer and Holzman	Russia	117	74	63.2	21	18.0
1933	Tomson	Esthonia	166	75	45.2	54	32.5
1933	Avdakov	Russia	728	293	40.2	189	25.9
1935	Sayago et al.	Spain	110	29	26.4	3	2.7
1936	Markó	Hungary	300	45	15.0	75	25.0
1936	Franz	Germany	133	46	34.9	30	22.8
1938	Mándi	Hungary	504	126	25.0	206	40.9
Totals (16 reports)		7	4,086	1,408	34.4	842	20.6

TABLE IV

OTHER ARTIFICIAL PNEUMOTHORAX CASES REPORTED AS "CURED"

INCOMPLETE INFORMATION

YEAR REPORTED	AUTHORS	COUNTRY	TOTAL NUMBER OF CASES	"CURED"	
				NO.	%
1913	Brauer and Spengler	Switzerland	88	23	26
1920	Schwenkenbecher	Germany	100	15	15
1920	von Muralt	Switzerland	70	12	17
1923	Unverricht	Germany	142	52	37
1923	Spengler	Switzerland	44	14	32
1923	Carpi	Italy	66	22	34
1924	Naveau	France	534	165	31
1925	Bernard et al.	France	201	40	20
1926	Schröder and Michelson	Germany	115	43	37
1926	Neumann and Wolf	Switzerland	149	98	66
1927	Weicksel	Germany	119	36	30
1927	Maendl	Austria	322	68	21
1927	Vulfovič	Russia	196	16	8
1928	Brühl	Germany	72	22	31
1928	Moos and Davidson	Germany	218	57	26
1931	Wiessner and Wolff	Germany	121	16	13
1932	Tatanis	Greece	444	75	17
1936	Kornacher	Germany	571	263	46
Totals (18 reports)		7	3,572	1,037	29

slightly less than one-third of all patients were considered cured and that over one-third died. Only about one-half of those still living were cured.

The results with pneumothorax treatment in sixty patients at the University of Chicago clinics during the past twelve years (which are presented in this paper) have been subdivided into groups of terminated and unterminated collapse. Under the heading "Cured," only such patients were listed who had been observed for two years or more fol-

TABLE V

SUMMARY OF ALL RESULTS OF ARTIFICIAL PNEUMOTHORAX THERAPY

NINETY-NINE REPORTS FROM EIGHTEEN COUNTRIES

	REPORTED CURED		DEAD		TOTAL NUMBER OF CASES	
	NO.	%	NO.	%	NO.	%
Acceptable Standards	2,358	39.8	2,298	38.8	5,925	26.7
Partially Adequate Standards	2,196	25.5	3,251	37.7	8,625	38.8
Inadequate Standards	1,408	34.4	842	20.6	4,086	18.4
Total, Complete Reports	5,962	32.0	6,391	34.3	18,636	83.9
Incomplete Reports	1,037	29.0			3,572	16.1
Grand Total, Cures	6,999	31.5			22,208	100.0

TABLE VI

SUMMARY OF "LATE RESULTS" OF ARTIFICIAL PNEUMOTHORAX ACCORDING TO FINAL REPORTED STATUS, 18,636 CASES

	PERCENTAGE OF LIVING	PERCENTAGE OF TOTAL
Living:		
Reported cured	48.7	32.0
Not cured	51.3	33.7
Total	100.0	65.7
Dead:		34.3
Total		100.0

lowing re-expansion of the lung and the other criteria of cured disease were applied rigidly. The other classifying terms which can be found in Tables VII and VIII were applied on the basis of the following definitions:

Apparently cured:	One to two years' observation after re-expansion.	In addition to the other criteria given for "Cure."
Arrested:	Less than one year's observation after re-expansion.	
Apparently arrested:	Lung still collapsed but patient clinically well, *or* lung re-expanded, with minor (pleural) complications.	
Unimproved:	Persisting evidence of cavitation, with or without symptoms of activity.	
Progressive:	Persisting symptoms of activity, extension of the tuberculous processes on x-ray examinations.	

These definitions do not conform in all details to the classifications of the National Tuberculosis Association, but it seems to us that persistent excavation is more important than the state of symptoms and even more than the extent of the lesion. Furthermore, the state of a lesion should be qualified by the period of time during which it has been observed.

TABLE VII

RESULTS OF ARTIFICIAL PNEUMOTHORAX THERAPY AT THE UNIVERSITY OF CHICAGO CLINICS IN SIXTY PATIENTS FOLLOWED ONE TO TWELVE YEARS

	TERMINATED CASES		UNTERMINATED CASES		TOTAL	
	NO.	%	NO.	%	NO.	%
Cured	19	44.2	0	0.0	19	31.7*
Apparently cured	2	4.7	0	0.0	2	3.3
Arrested	16	37.2	0	0.0	16	26.7†
Apparently arrested	1	2.3	14	82.4	15	25.0
Total, Favorable	38	88	14	82	52	87
Unimproved	0	0.0	3	17.6	3	5.0
Progressive	1	2.3	0	0.0	1	1.6
Dead	4	9.3	0	0.0	4	6.7
Total, Unfavorable	5	12	3	18	8	13
Total	43	100	17	100	60	100

*Two cases cured by thoracoplasty; one cured case had thoracoplasty for late pleural complications.

†One case arrested by thoracoplasty, and one by extrapleural pneumothorax; four arrested cases had thoracoplasty for late pleural complications.

TABLE VIII

RESULTS OF TERMINATED CASES ACCORDING TO INITIAL STATUS

UNIVERSITY OF CHICAGO CLINICS

	MINIMAL		MODERATELY ADVANCED		FAR ADVANCED		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Cured	0	0.0	7	50.0	12	42.8	19	44.2
Apparently cured	0	0.0	0	0.0	2	7.1	2	4.7
Arrested	1	100.0	7	50.0	8	28.6	16	37.2
Apparently arrested	0	0.0	0	0.0	1	3.6	1	2.3
Unimproved	0	0.0	0	0.0	0	0.0	0	0.0
Progressive	0	0.0	0	0.0	1	3.6	1	2.3
Died	0	0.0	0	0.0	4	14.3	4	9.3
Total	1	2.3	14	32.6	28	65.1	43	100

It would have been misleading to estimate the proportion of our pneumothorax patients from the total number of patients seen in the chest clinic because the majority of the latter are examined in consultation only or are sent to sanatoria after completion of the diagnosis, many with the recommendation of collapse therapy. This also explains the small number of patients on whom we feel justified in making a report. On the other hand, the possibility of retaining for hospitalization only those patients who suit the purposes of a research and teaching institution results in a highly selected group which goes far in explaining the favorable results as well as the low number of cases of progressive disease and deaths. We are in the happy position of being able to reject desperately advanced cases in which other institutions, especially the public sanatoria, have to make last attempts with some form of collapse therapy. It should be added, however, that with two ex-

ceptions, all of our patients in whom treatment is terminated had cavernous tuberculosis with positive sputum, and two-thirds were classified initially as far advanced.

TABLE IX

DURATION OF PNEUMOTHORAX AND INSTITUTIONAL CARE OF TERMINATED CASES AT THE UNIVERSITY OF CHICAGO CLINICS

DURATION	NUMBER OF CASES OF PNEUMOTHORAX	NUMBER OF PATIENTS UNDER INSTITUTIONAL CARE
1 to 6 mo.	2	7
6 to 12 mo.	8	8
1 to 2 yr.	8	16
2 to 3 yr.	7	8
3 to 4 yr.	4	3
4 to 5 yr.	7	0
Over 5 yr.	7	1
Total	43	43
Average duration	34 mo.	19.5 mo.

Besides the selection of the group, the low incidence of unimproved and progressive disease is attributed chiefly to two factors: (1) the insistence on extensive institutional care with several months of complete bed rest during the initial stage of collapse (Table IX, tabulation of the duration of hospital treatment, the average of which was 19.5 months), (2) the timely decision on surgical collapse when air collapse seemed impossible or unlikely to succeed.

A considerable number of patients in whom a short-term pneumothorax attempt was followed by surgical collapse are not included in this report. This explains the low figure of only nine patients (15 per cent) in whom pneumothorax was replaced by thoracoplasty.

In recent years the average duration of pneumothorax treatment has been increasing steadily. It has been realized that collapse of only one year's duration or a little more is not likely to achieve a permanent cure in the average patient. At present the average minimum duration seems to be about three years. Consequently, the treatment has not only become increasingly costly, but the danger of late pleural infections and other complications is enhanced. The patient who has been under treatment for years and has, at least to some extent, returned to normal life and work is not as cautious about his condition as he was in the earlier periods of collapse. It is distressing when, after years of sickness, expense, and uncertainty about the future, the necessity of surgical interference has to be faced. While it is true that some patients whose general condition in the beginning would not allow extensive operation can be prepared for it by preliminary pneumothorax, there are equally many in whom an air collapse, although doomed to failure from the beginning, is continued, with no result but loss of time. The question as to when pneumothorax therapy should be con-

sidered ineffective and be replaced by more active methods should not be approached with a fear of the permanence of surgical collapse or of the dangers of operative procedures. With the amazing advances in chest surgery, surgical collapse has lost the terrors experienced by patients years ago. The inconvenience and cost of many years of pneumothorax treatment, together with the ever present danger of complications, are powerful arguments for early surgical intervention whenever the efficacy of air collapse becomes dubious.

The close cooperation and happy understanding between the internist and the surgeon are the best guarantee for the successful interlocking of all forms of collapse.

SUMMARY

The indications for artificial pneumothorax treatment need to be more sharply delineated.

The tuberculous cavity is the most important factor in the indication for collapse.

The success obtained with artificial pneumothorax can be judged more accurately by applying strict criteria to the results.

In addition to other criteria, at least two years should elapse after re-expansion of the lung before one considers a patient as cured.

Rest treatment in combination with collapse is an absolute necessity. Ambulatory initiation of pneumothorax lacks the basis of all treatment of tuberculosis and is dangerous.

Surgical collapse should follow unsuccessful air collapse as soon as the failure of pneumothorax to obliterate excavation has become evident.

The world's literature on results with pneumothorax treatment is reviewed.

The results in sixty patients treated by artificial pneumothorax at the University of Chicago clinics are presented.

We are indebted to Dr. Byron F. Francis, Medical Director of the Riverton Sanatorium, Seattle, Wash., who during his connection with the University of Chicago, participated in the treatment of most of the patients reported in this paper.

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DISCUSSION

DR. DEAN B. COLE, Richmond, Va.—I do not believe that Dr. Bloch saw a paper that we read before the National Tuberculosis Association in 1935. If he wants it, I will send him a reprint. We reported in detail on patients who were ambulatory while treated by pneumothorax. Many of these patients are well after working fifteen years. We plan to report on what has happened to all of these patients. It is not that we think one should do something to every patient and send him on his way, but, as most of you know, we are opposed to big relief rolls. We believe that if one can put people back to work, that is where they belong. As a matter of fact, much of what is being done in this country is being done by people who are not entirely well.

The treatment of tuberculosis is not incidental and should not be accidental. We have had a long struggle in Virginia and at last have put over a program. Dr. Stafford and other members of the state sanatoria are here. If anyone wants to know about this program, ask them. We believe sanatoria are fine hospitals but poor boarding houses. We put that into application. You do not have to keep patients in sanatoria forever to get them permanently well.

There are other factors in tuberculosis besides collapse and rest, and besides this and besides that. I thought that perhaps we had a benign type of bacillus in Virginia—maybe Chicago has it too—because our patients get well with a different program. I do not mean that they have not had rest, but our rest program and sanatorium residence have been greatly shortened. In Virginia between 450 and 500 indigent pneumothorax patients are being treated by private physicians. The state pays the physician a nominal fee to take care of them. I understand from Dr. Harper, who has charge of this program, that it is most satisfactory. A few years ago you heard it explained on every side that the general practitioner, who was doing everything else, sometimes major surgery, could not do pneumothorax. It seems to me that we all have to compromise, and that there is somewhere in between.

DR. HENRY W. LEETCH, Saranac Lake, N. Y.—I want to thank Dr. Bloch for doing something that I think has been very necessary, to protect us medical men and our pneumothorax treatments against the increasing attacks of surgeons. In the last few years, a lot of us have been questioning pneumothorax and the value of it, and certainly for myself, I look on pneumothorax now as a treatment, in its

long-time implications, as serious as thoracoplasty. However, we cannot drop pneumothorax, whether we want to or not. There are cases unsuitable for thoracoplasty that are suitable for pneumothorax, and we will, of course, save many lives with it.

The two points that Dr. Bloch brought out that pleased me immensely were, first, his conservative attitude toward pneumothorax, his realization that nature is still able to cure a great deal of tuberculosis without any outside aid; and second, his calling to our attention what I think is the too widespread, indiscriminate use of pneumothorax without any regard to the criteria for giving it, but using it for every case that comes under one's care. If Dr. Bloch's paper will make us stop this blanket use of pneumothorax without regard to the indications for and against its use, it will go far toward putting pneumothorax into its proper relationship with the other forms of collapse therapy.

DR. BLOCH.—I have nothing further to say, except to remind Dr. Cole that we stated specifically at the beginning of this paper that we were not engaged in public health work, that we realized the compromises which have to be made, but that we wanted to confine ourselves strictly to medical standards only.

POLYPOID BRONCHIAL TUMORS*

With Special Reference to Bronchial Adenomas

Alfred Goldman, M.D., and H. Brodie Stephens, M.D.
San Francisco, Calif.

POLYPOID bronchial tumors are those neoplasms which grow as projections within the bronchial lumen and are usually visible through the broncoscope. Bronchial adenomas, which are a type of polypoid tumor, have an unusual form of growth. As they enlarge, both an endo- and extrabronchial tumor is usually produced (Figs. 1-8).

Until a short time ago, all invasive polypoid bronchial tumors were believed to grow rapidly and to metastasize. Only since 1932[1] have polypoid bronchial adenomas been separated, clinically and pathologically, from the other polypoid tumors to form a new clinical entity—a polypoid bronchial tumor which may be locally invasive but which, from our experience, never metastasizes distantly and hence can be cured by surgical removal.

The evolution of the definite distinction of these bronchial adenomas from carcinomas and distantly metastasizing tumors has three periods. The first began in 1882 with the publication of Mueller's[2] case, and ended in 1932 with the report on bronchial adenomas by Wessler and Rabin.[1] The first period may be described as the period of post-mortem recognition[3-9] of bronchial adenomas, although in 1930 Kramer[10] reported the first case clinically and bronchoscopically diagnosed. From 1932 until 1938 occurred the period of clinical recognition and treatment.[11-15] Overlapping part of this period and continuing into the future exists a period of development of rational therapy, based upon newer knowledge of the natural and therapeutic life history of these tumors.[16-19]

Since bronchial adenomas are polypoid in form and amenable to surgical removal, and comprise some 6[15] to 10[17] per cent of all bronchial tumors and 25 per cent of all resectable bronchial tumors,[17] it becomes important to differentiate them (the adenomas) particularly from carcinomas in order to select the proper therapy. Three types of polypoid tumors may be distinguished:

Metastasizing polypoid tumors (carcinoma);
Locally invasive but not distantly metastasizing polypoid tumors (adenoma);

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*It is to be regretted that there has been so long a delay in the publication of this article. As originally submitted, the manuscript was so long that sufficient space in the JOURNAL was not available. The delay has, therefore, been due to the revision necessitated by the contraction of the article. ED.

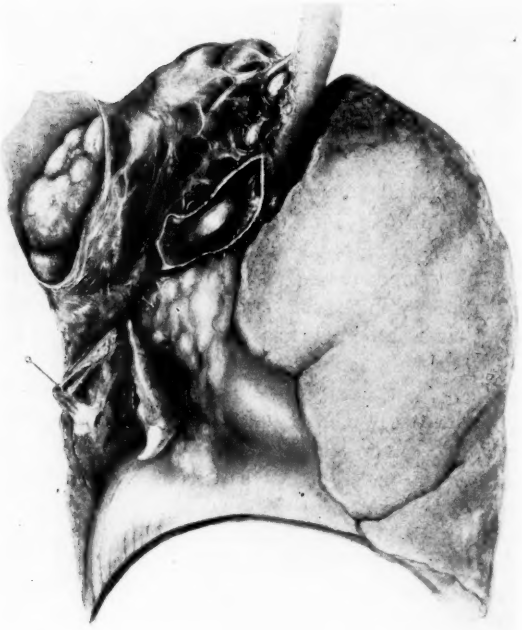

Fig. 1.—I. K., Case 1 (see Table I). Post-mortem specimen showing large adenoma obstructing right stem bronchus and producing pressure atrophy of entire right upper lobe.

Fig. 2.—F. M., Case 3. Post-mortem specimen showing encapsulated bronchial adenoma.

Noninvasive, nonmetastasizing, purely local polypoid tumors (fibroma, lipoma, myoma, and others).

The importance of this reclassification and the recent separation of adenomas from carcinomas is demonstrated by a review of some of the

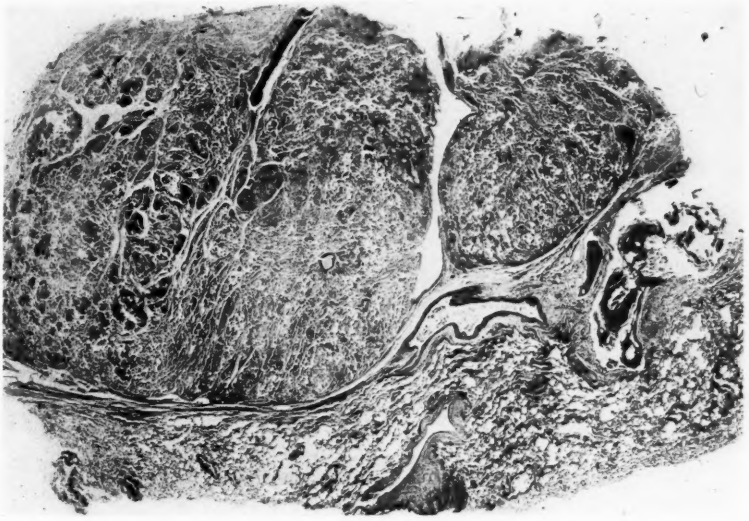

Fig. 3.—F. M., Case 3. Photomicrograph (×5) of section of the entire tumor. Note the cartilaginous ring surrounded by tumor, at the top of the figure.

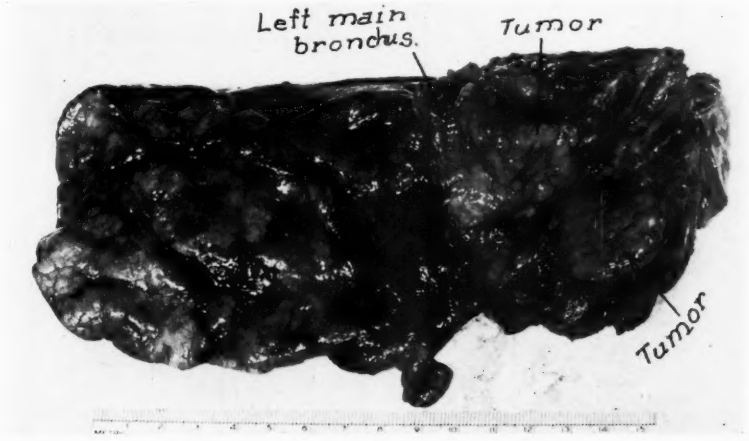

Fig. 4.—H. L., Case 4. Left pneumonectomy specimen showing well-localized extrabronchial tumor and obstructing endobronchial tumor in the left main bronchus.

publications which resulted from their confusion. It seems most probable that certain reports of the successful removal of carcinoma of the lung by means of the bronchoscope,[12, 20-24] of the cure of carcinoma of

TABLE I

CASE	AGE AT ONSET OF SYMPTOMS (YR.)	SEX	LOCATION OF TUMOR	MORPHOLOGY AND SIZE*	DURATION UNTIL DIAGNOSIS OF TUMOR (YR.)	DURATION SINCE DIAGNOSIS UNTIL PRESENT TIME OR DEATH (YR.)	TOTAL DURATION OF DISEASE (YR.)	COMPLICATIONS	TREATMENT	PRESENT STATUS† AND CAUSE OF DEATH
1 I. K.	28	F	Right stem	Endo-extrabronchial, 13.5	20	20	20	Atelectasis; abscess; empyema; parenchymal pressure atrophy; hemiplegia	Drainage of empyema and abscess	Died 18 years after drainage operations, from pulmonary suppuration. No metastasis. Post mortem.
2 J. B.	22	F	Right stem	Endo-extrabronchial, 5.0	13	12	25	Cystic bronchiectasis	Bronchoscopic removal; x-ray	Local recurrence 12 years postoperatively. Complete obstruction of right stem bronchus. General condition good. No metastasis.
3 F. M.	50	M	Right upper lobe	Endo-extrabronchial, (periph.), 4.0	?	4	4	Bronchial pressure atrophy	None	Died of ruptured aortic aneurysm 4 years postoperatively. Post mortem.
4 H. L.	48	F	Left stem	Endo-extrabronchial, 5.0	6	9	15	Atelectasis; spontaneous fractured ribs	Pneumonectomy	General condition good 2 years postoperatively. No metastasis.
5 I. W.	46	M	Left lower lobe	Endo-intramural, 3.0	1	5	6	Atelectasis; abscess; empyema; brain abscess	Bronchoscopic radium; drainage of empyema	Died 5 years after treatment. Residual tumor post mortem. No metastasis.

*Longest diameter in centimeters. When no pathologic specimen was available, diameter was estimated from bronchoscopic and x-ray studies.
†On Oct. 1, 1940.
‡Performed by Dr. L. Eloesser.

6 H. G.	32	F	Right stem	Endo-extra-bronchial, 6.5	8	8	16	Empyema; abscess; hemorrhage; atelectasis; parenchymal pressure atrophy	Drainage of empyema and abscess; x-ray	General condition good. Tumor still obstructs right lower lobe and right middle lobe, slowly enlarging; 8 years after radiation therapy.
7 J. S.	27	M	Right stem	Intramural, 2.0	6	2/12	6 2/12	Atelectasis; abscess; postoperative hemorrhage	Bronchoscopic high frequency cauterization	Died 1 week after treatment. No residual tumor. Cerebral emboli; pulmonary hemorrhage. Post mortem.
8 E. D.	13	M	Left stem	Endo-bronchial, 2.0	4	2	6	Atelectasis; pneumococcus Type III; bronchiectasis	Bronchoscopic removal, piecemeal	General condition good. No recurrence 2 years after treatment. Bronchiectasis decreased.
9 J. G.	23	M	Left stem	Endo-intramural, 2.5	1	1/12	1 1/12	Atelectasis; bronchiectasis; postoperative empyema	Pneumonectomy	Died 1 month postoperatively. Postoperative empyema. No metastasis.
10 F. J.	20	F	Left lower lobe	Endo-extra-bronchial, 2.5	6	2	8	Bronchiectasis	Lobectomy	General condition good 2 years postoperatively. Extrabronchial tumor left in stump. No metastasis.
11 C. R.	46	M	Left stem	Endo-extra-bronchial, 2.5	2	2	4	Atelectasis; bronchiectasis; interstitial pneumonia; postoperative empyema	Pneumonectomy after endobronchial removal	General condition good 2 years postoperatively. No metastasis.
12 S. J.	49	M	Right upper lobe	Endo-extra-bronchial, 7.5	5/12	2 1/12	2 6/12	Pressure atrophy	X-ray	General condition good. Characteristic patterns not present in biopsy. No metastasis.
13 A. B.	10	F	Left stem	Endo-intramural, 2.5	22	1 6/12	23 6/12	Atelectasis; bronchiectasis	Bronchoscopic removal, piecemeal	General condition good. Residual intramural tumor present. No metastasis. Minimal symptoms from bronchiectasis.

TABLE I—CONT'D

CASE	AGE AT ONSET OF SYMPTOMS (YR.)	SEX	LOCATION OF TUMOR	MORPHOLOGY AND SIZE*	DURATION UNTIL DIAGNOSIS OF TUMOR (YR.)	DURATION SINCE DIAGNOSIS UNTIL PRESENT TIME OR DEATH (YR.)	TOTAL DURATION OF DISEASE (YR.)	COMPLICATIONS	TREATMENT	PRESENT STATUS† AND CAUSE OF DEATH
14 G. D.	33	F	Left lower lobe	Endo-extra-bronchial, (periph.), 7.0	10	1 6/12	11 6/12	Pressure atrophy; atelectasis	Lobectomy	General condition good. No metastasis 10 months after treatment.
15 J. G.	21	F	Right stem	Endo-extra-bronchial, 5.0	6/12	10 6/12	1 4/12		Lobectomy‡	General condition good 8 months after treatment. No metastasis.
16 W. C.	46	F	Right lower lobe	Endo-extra-bronchial, (periph.), 4.0	5	5	10		X-ray	General condition good. No enlargement of tumor mass for 5 years. Characteristic patterns not obtained in biopsy.
17 C. B.	34	F	Right stem	Endo-intra-mural. Size undetermined	2	5	7	Atelectasis; bronchiectasis	X-ray	General condition good. Atelectasis persists. Characteristic patterns not obtained in biopsies.
18 D. W.	41	F	Left upper lobe	Endo-extra-bronchial, 5	1	5	6	Atelectasis	X-ray	General condition good. Atelectasis persists. Characteristic patterns not obtained in biopsies.

the lung by pneumonectomy,[25-28] or of deep x-ray therapy[29, 30] actually refer to cases of adenoma.

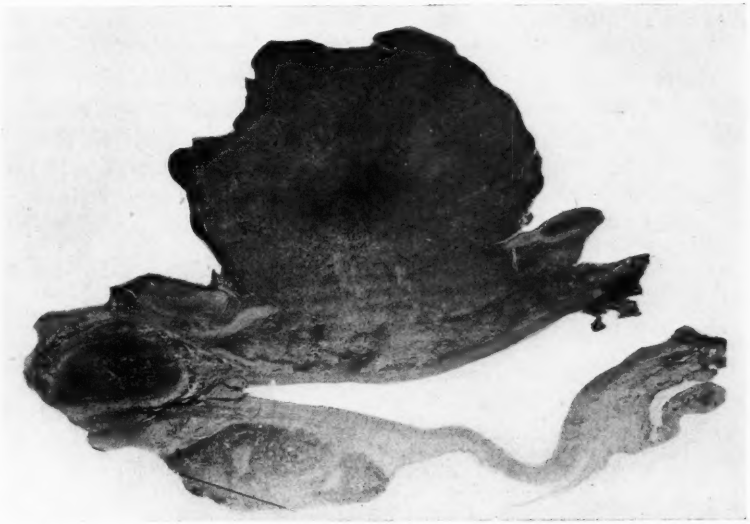

Fig. 5.—J. G., Case 9. Photomicrograph (×5) of post-mortem specimen showing extension of the adenoma in the direction of the mediastinum between two cartilaginous rings. Note the large intramural portion. Neighboring lymph nodes contain no metastases.

Fig. 6.—F. J., Case 10. Lobectomy specimen showing cystic bronchiectasis limited to obstructed portion of the left lower lobe.

The various names by which the clinical entity now termed "bronchial adenoma" has been designated have added still further to the confusion. Ephraim in 1911[31] termed these tumors "sarcoma, of alveolar pattern"[32]; Kreglinger (1913),[5] "cylindrical cell carcinomas"; Geipel (1931),[9] "basal cell cancers"; Wessler (1932),[1] "benign bronchial adenomata"; Kernan (1935),[24] "carcinoids"; Moersch (1935),[23]

"adenocarcinomas"; Clerf and Crawford (1936),[33] "benign glandular tumors"; Zamora and Schuster (1937),[13] "vascular adenomata"; Welt and Weinstein (1937),[34] "endotheliomas"; and finally, Womack and Graham (1938),[16] "mixed tumors of the lung." Yet undoubtedly each of these authors referred to the same type of tumor.

The age of the patient at the onset of symptoms of adenoma is strikingly different from that of patients with carcinomas. In our group of eighteen patients (see Table I) with bronchial adenomas, eleven, or 60.5 per cent, had symptoms before the age of 40, in contrast to only 13 per cent of those with carcinomas as shown in Fischer's[35] large series and 11 per cent in Brunn's.[36]

Fig. 7.—C. R., Case 11. Pneumonectomy specimen of the left lung showing organizing interstitial pneumonia of the left lower lobe. There is no tumor in the specimen and no metastases in the neighboring lymph nodes examined. Preoperative endobronchial removal.

The distribution by sex is likewise in marked contrast to that in carcinomas. In our eighteen cases of adenoma, eleven, or 60.5 per cent, were females, whereas only 25 per cent of the carcinomas occurred in females in Simpson's[37] and El Gazayerli's[38] series. In our last 111 cases of carcinoma, only 9 per cent occurred in females.

In prognosis and duration of life also, patients with adenomas present a marked contrast to those with carcinomas. If all cases of probable adenoma which have been reported as carcinoma are excluded, a few probable "five-year cures" of true bronchial carcinoma remain.[39-42] The prognosis for patients with adenomas, on the other hand, is very

good and many "five-year cures" have been reported.[1, 24, 43] In our series, for example, all of the patients but three (16.5 per cent) lived more than three years after the onset of symptoms; thirteen (71.5 per cent), more than five years; and six (33.3 per cent), more than ten years. These figures are noteworthy since in Brunn's[36] cases of carcinoma only 4 per cent of 297 patients survived three years or longer.

The symptoms and clinical course of bronchial adenoma are related to three peculiarities of this tumor's life history: first, location of the adenoma in a major bronchus; second, its slow growth; and third, its vascularity.

Fig. 8.—G. D., Case 14. Left lower lobectomy specimen showing pressure atrophy of lung surrounding large adenoma. Bronchoscopic removal was attempted unsuccessfully preoperatively.

Any lesion encroaching upon the lumen of a large bronchus gives rise to symptoms of bronchial obstruction, and the first symptoms of these tumors result from disturbance in the transference of air along the large bronchial tubes. Wheezing, "asthma," irritating nonproductive cough, dyspnea, transient chest pains, "choked-up sensations," and respiratory postural discomfort are thus the initial symptoms to appear. These are often so indefinite or transient as to be entirely overlooked unless they are inquired for very carefully. When air becomes completely shut off from the alveoli distal to the tumor, atelectasis results; this occurred in seventeen of our eighteen patients. On the other hand, when air is entrapped distal to the tumor, emphysema occurs.

As the endobronchial portion of the tumor grows, the bronchial obstruction also interferes with the drainage of bronchial secretions[44];

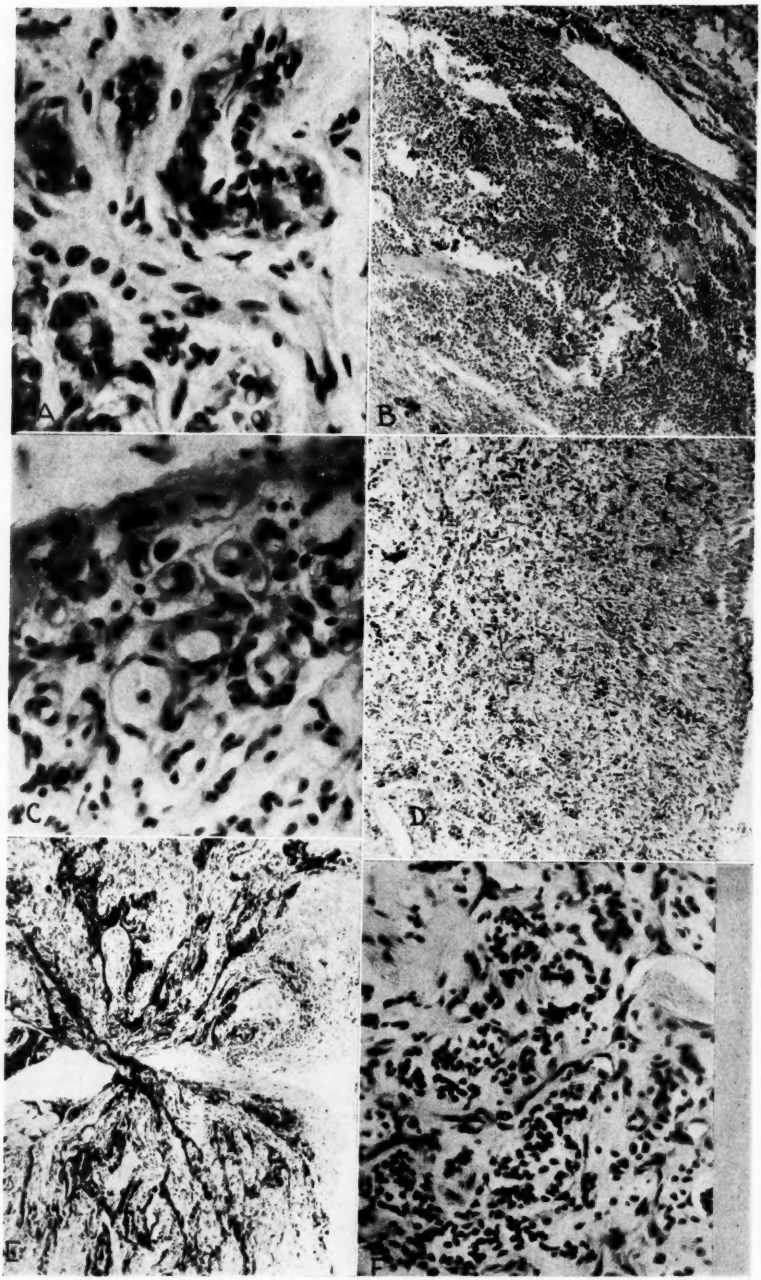

Fig. 9.—(See opposite page for legend.)

consequently, the next symptoms to appear are those of pulmonary suppuration. Recurring "pneumonia," or so-called "drowned lung" caused by the obstructive atelectasis, are most common; but empyema, abscess, and bronchiectasis are frequent (see Table I). Ten of our patients had marked symptoms of pulmonary suppuration, and all had marked bronchial occlusion. The remaining eight had only slight symptoms of suppuration although bronchial obstruction was present. In four of these the tumors were located in the upper lobes, and in four, in the lower lobes. Acute and dangerous suppurative sequelae may occur, such as lobar pneumonia, pulmonary abscess, empyema, and metastatic brain abscess. Bacteriologic studies disclosed that there were seven cases of aerobic pyogenic infection, five cases of anaerobic infection, and one case each of pneumonia Type IV and pneumonia Type III, with the clinical picture of a typical lobar pneumonia, and streptothrix infection, with metastases to the brain. When death occurs, it usually results from suppuration secondary to the tumor, or, more rarely, from complications following treatment.

On the other hand, the slow growth of these tumors allows time for permanent chronic inflammatory changes to occur in the lungs and pleura. Thus are produced chronic suppuration and toxemia which give rise to easy fatigue, low-grade fever, chronic cough, sputum, pleuritic pains, dyspnea on slight exertion, anemia, anorexia, and all the symptoms usually associated with pulmonary tuberculosis. In six, or one-third, of our cases, the diagnosis of pulmonary tuberculosis had been made, and these patients had been under treatment for tuberculosis for periods ranging from several months to several years. The true diagnosis of bronchial adenoma was unrecognized. After many years an astonishing degree of resistance seems to be acquired, so that the smouldering infection which may involve even an entire lung flares up less often and produces less disability (Cases 1, 2, and 13, and Fig. 12, *A* and *B*).

The cardinal symptom of bronchial adenoma is the pulmonary hemorrhage associated with the extreme vascularity of these tumors (Figs. 9, *B* and *C*, and 10*D*). The hemorrhages are characteristically sudden in onset and termination, bright red in color, profuse even to the extent of producing shock, unprovoked by cough or exercise, and in women frequently occur during the menstrual period. This hemorrhage probably arises from the tumor itself. A second type of hemorrhage, asso-

Fig. 9.—Characteristic bronchoscopic biopsy specimens.

A, F. J., Case 10. (×750.) Note the pyknotic nuclei and the indefinite pattern. Although the diagnosis of adenoma was made from this section, it was made with some doubt.

B, G. D., Case 14. (×120.) Note the large vascular spaces filled with blood, lying among the tumor masses. Such a biopsy may be called hemangioendothelioma.

C, A. B., Case 13. (×750.) Area of biopsy showing an angiomatous pattern.

D, J. G. O., Case 15. (×120.) Area of biopsy showing inflammatory granulation tissue.

E, E. D., Case 8. (×120.) Shows the atypical appearance of crushed biopsies.

F, H. L., Case 4. (×120.) Biopsy first diagnosed angioendothelioma. Note the absence of uniform arrangement of cells, and the pyknosis.

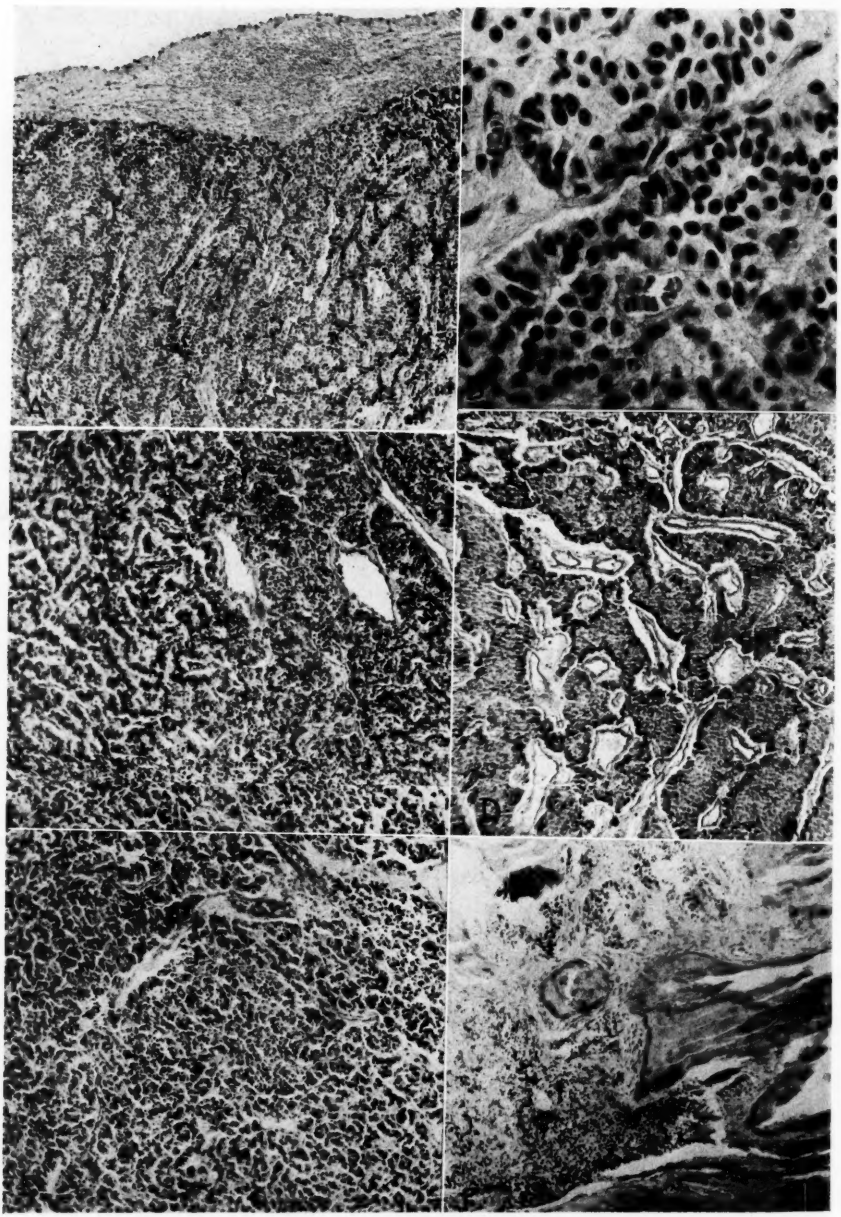

Fig. 10.—(See opposite page for legend.)

ciated with the distal suppuration, is just as frequent. It is composed of dark blood, often clotted and mixed with pus, is induced by cough and exertion, and is followed by bloodstreaked sputum for several days. Pulmonary hemorrhage was a cardinal symptom in twelve, or 66.6 per cent, of our patients. This, however, is very rarely the immediate cause of death. All the symptoms described are related to the endobronchial portion of the tumor; few severe symptoms are produced by the extrabronchial or mural portions, even though considerable parenchymal pressure atrophy occurs.

Roentgenologically (Fig. 11, *A* to *E*), the appearance is bizarre, but characteristically lobar atelectasis is present.[45, 46] Disturbances in aeration characterize the picture, so that varying degrees of emphysema and atelectasis[47, 48] are present. A marked shift of the mediastinum, thick pleurae, cystic whorls, and abscess cavities represent the results of the suppuration. The tumor itself is demonstrated only occasionally, usually because of the inflammatory changes overlying it. The ordinary x-ray films of the cases in which an extrabronchial extension was actually seen in the autopsy or surgical specimen frequently failed to demonstrate the true extent of the tumor. This is usually due to atelectatic lung surrounding the tumor, to neighboring pneumonitis, or to a thickened pleura, all of which produce a density that clouds the true outline of the adenoma. In the occasional case where the tumor arises in a branch bronchus, a lobulated or rounded tumor mass may be visualized on the x-ray film. Such a mass may simulate a metastatic deposit rather than a primary tumor. In only four of our eighteen cases could we see a discrete tumor mass in the ordinary x-ray film.

We have observed that tomography will delimit the true morphology, the relation to surrounding structures, and the extent of the extrabronchial portion even when other roentgenologic studies either failed to disclose a discrete mass or to show its relation to the bronchial lumen (Fig. 12, *A* and *B*). Definite evidence of infiltration along the bronchial wall, in the form of an obstructing or stenosing lesion, and extrabronchial pressure may be obtained. Frequently these tomographic findings, taken together with the bronchoscopic examination, have been

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Fig. 10.—Typical patterns obtained from post-mortem or pulmonary resection specimens. These photographs should be compared with those of Fig. 9.

A, G. D., Case 14. (See Fig. 8.) (×120.) Columns of uniform cells extending toward the fibrous tissue capsule. The bronchial mucosa has been denuded. Note the relative absence of pyknotic nuclei when compared to the bronchoscopic biopsies.

B, G. D., Case 14. (×750.) Section of the surgical specimen showing both cylindromatous and alveolar patterns.

C, H. L., Case 4. (See Fig. 4.) Section of the extrabronchial tumor. Note the marked difference in the cellular patterns obtained by the biopsies and the surgical specimen. Note again two different patterns on the same section.

D, H. L., Case 4. (×120.) Note the mosaic pattern made up of large groups of cells and prominent vascular stroma. This section of the tumor appears markedly different from that seen in *C*.

E, I. K., Case 1. (See Fig. 1.) (×120.) Note the mosaic pattern made up of small groups of cells. This pattern was uniform throughout all the sections made of this tumor.

F, F. J., Case 10. (See Fig. 6.) (×120.) Formation of osteoid tissue in extrabronchial portion of the tumor.

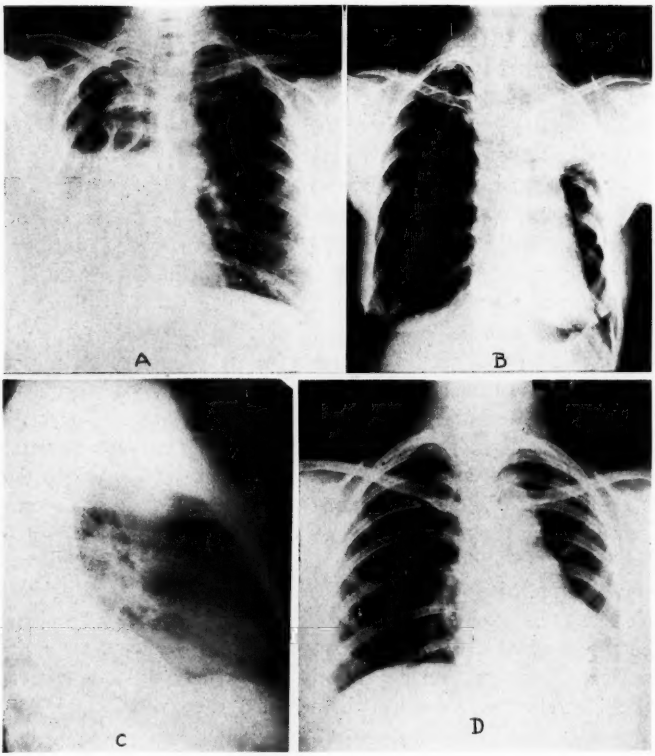


Fig. 11.—Typical x-rays of bronchial adenoma.

A, H. G., Case 6. Aug. 5, 1937. Posteroanterior view. Tumor now of thirteen years' duration. Note that, because of the overlying density, the tumor itself is not visible.

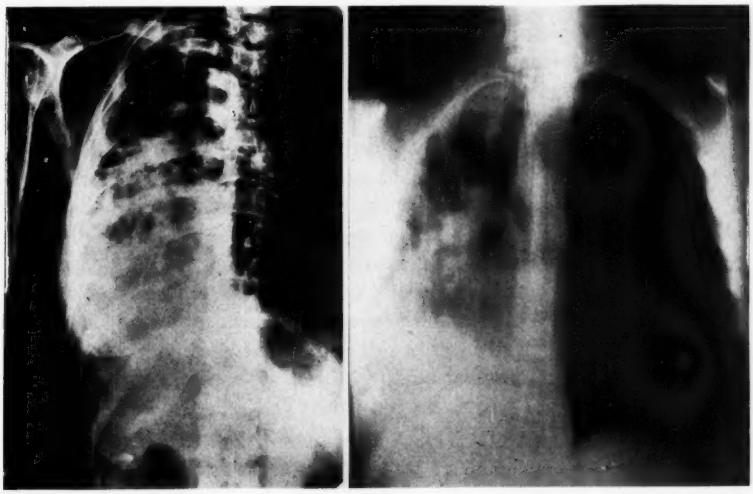
B, H. L., Case 4. Aug. 25, 1938. Duration now thirteen years. Note the atelectasis of the left upper lobe, and the healed fractures of the ribs.

C, E. D., Case 8. May 3, 1938. Left lateral view. Clinical and x-ray diagnosis was lobar pneumonia. Note the atelectasis of the left lower lobe.

D, G. D., Case 14. April 18, 1939. Posteroanterior view. Atelectasis of the left lower lobe.

E, G. D., Case 14. April 18, 1939. Left lateral view. Note the failure to delineate a tumor mass, or even atelectasis of the left lower lobe. Compare this x-ray with Fig. 8.

of great aid in differentiating adenomas from carcinomas. As we might expect, an extrabronchial adenoma appears discrete, well demarcated, and smooth in outline; but a carcinoma usually shows a shadow blending with the opacity of inflammatory or atelectatic areas. Tomography is the most important new diagnostic aid since the advent of the bronchoscope. This procedure should be performed routinely for all tumors of the lung, and particularly for any tumor suspected to be an adenoma. Shadows cast by areas of occult atelectasis, with or without adenoma, blend with the mediastinum and spine so that they are easily overlooked in the plain x-ray films but are strikingly depicted in the tomograms.



A. *B.*

Fig. 12.—Tomographic studies.

A, J. B., Case 2. Feb. 15, 1940. Hard shot. Note the whorls appearing throughout the right lung, and the absence of any definite tumor mass.

B, J. B., Case 2. Feb. 4, 1940. Posteroanterior view 8 cm. from the back. The endobronchial tumor filling the right stem bronchus with larger extrabronchial lobar extensions is distinctly outlined.

Bronchography, particularly with "endobronchial probing," is valuable in determining the level of the bronchial obstruction and the condition of the distal bronchi. When lipiodol is prevented from flowing into the distal lung before endoscopic removal of an adenoma, a repeated bronchogram afterward frequently discloses marked bronchiectasis in the distal lung. Initial bronchograms are characterized by a wide column of lipiodol with a smooth concavity at the distal end and also along one border (seen best in the lateral view), occupying the whole of a stem bronchus.

The bronchoscopic image is that of a soft or firm mass or polyp, whitish, pink, or purple, and, if of long duration, indurated and hard. These tumors are covered with mucosa, and occasionally vessels traverse

the bosselated surface. Their attachment to the bronchial wall varies from a few millimeters to 2 cm. in diameter, and when this tumor can be removed endobronchially, its stalk may be seen descending between the cartilaginous rings. Most often, however, the bronchus around the tumor is distended and its cartilages are thinned out or even absent. The bronchial wall may be so thin that it cannot be distinguished grossly. Frequently the endobronchial portions of these tumors grow in a proximal direction toward the trachea so that they fill the entire length of a stem bronchus. When they arise near the bifurcation of a stem bronchus, lobulations may extend into the branch bronchus on either side.

The bronchoscopic picture of an adenoma is usually distinctive enough to differentiate it from that of a primary bronchial carcinoma. In the latter there is ulceration and induration, with the characteristic "frozen" condition of the surrounding structures; and the carina may be narrowed in the anterior posterior diameter from metastatic lymph glands in the hilar area. Adenomas, on the other hand, are freely movable. Ulceration usually is not present, and there is no infiltration of the adjacent bronchial mucosa. Occasionally, when the adenoma is of the intramural type, presenting as a low, broad induration instead of a polypoid mass, the bronchoscopic differentiation is impossible. Hemorrhage gives another important bronchoscopic clue to the true diagnosis. We have frequently encountered rather severe bleeding from the adenoma with the least trauma, whereas the same amount of bleeding is unusual in the case of polypoid carcinoma.

Bronchoscopic removal of adenoma re-establishes the bronchial airway and also the drainage of distal infection, thus bringing about a dramatic and marked improvement of the patient. But, due to the intramural and extrabronchial extensions of these tumors, it is doubtful that every cell is removed by such treatment. Consequently, late recurrences can be expected frequently, although they may not be suspected for ten years or more (Case 2, J. B.). For this reason, patients treated bronchoscopically should always be followed by bronchoscopic examinations at intervals of no less than one year. In addition, the older tumors are so large and so adherent to the thinned-out bronchial walls that endobronchial removal is impossible and may bring about an unnecessary fatality.

Histologically (Figs. 9, *A* to *F*, and 10, *A* to *F*), bronchial adenomas are characterized by a uniformity of cell type, and absence of mitotic figures, and a tendency for the cells to be grouped. Covering the tumor is the mucosa, which usually undergoes squamous-cell metaplasia or denudation, and is separated from the epithelial portion of the tumor by a more or less dense membrane of fibrous tissue. Beneath this membrane the epithelial surface is highly vascular. The extrabronchial portion is covered by peribronchial connective tissue. Bone and cartilage

are found frequently. The cells are often arranged in patterns of different designs, giving at first glance the appearance of a wildly growing tumor. Columnar, alveolar, acinar, mosaic, medullary, and angiomatoid patterns occur. In some cases (F. M. and K. I.), the histologic pattern is uniform throughout the whole tumor. In others (H. L. and G. D.), the patterns vary a great deal in different parts of the tumor. Groups of cells may be found in the capsule, bronchial perichondrium, and neighboring alveoli. Blood and lymph vessel invasion has not been observed by us. The stroma may vary from a well-developed, reticular, delicate network containing the groups of cells, to a thickened or hyalinized one containing large vascular spaces.

Histologic diagnosis of adenoma from the material removed at bronchoscopic biopsy is not easy because the tissue obtained often is not deep enough within the tumor to show characteristic patterns. Squamous cell carcinoma, because of the squamous cell metaplasia present on the mucosal surface, or angioma due to the vascularity just beneath the connective tissue capsule, or inflammatory tissue when the epithelial surface has been traumatized—any of these may be diagnosed instead of adenoma. In the beginning, we had to convince the pathologist that the tissue seen represented adenoma rather than carcinoma, hemangioendothelioma, or inflammatory tissue. In doing this, we emphasized the importance of the clinical history.

While we favor the view that these tumors are of epithelial origin, arising from the epithelium of the ducts of the mucous glands, or that of the mucous glands themselves, this is a subject within itself and will be discussed in a future publication by our pathologist, Professor Charles Connor.

Bronchial adenoma must be differentiated from tuberculosis, malignant and benign polypoid tumors, and bronchiectasis. The similarity of the symptoms presented by patients with tuberculosis and adenoma has already been mentioned. In young females in whom tuberculosis is diagnosed and in whom no tubercle bacilli can be found, adenoma should be suspected, particularly if the history is of long duration, the cardinal symptom is hemoptysis, and the x-rays suggest atelectasis. Bronchial tuberculosis may produce a symptom complex similar to that described for adenoma, but the former disease is more progressive and usually tubercle bacilli can be found in the sputum or bronchial smears. Bronchoscopy, of course, usually tells the story. In the one condition an ulcerative process is seen, while with adenoma a tumor mass is present.

Because carcinoma and other malignant tumors may present as a polypoid tumor to the bronchoscopist, adequate biopsies with careful histologic interpretations are frequently necessary to bring about early diagnosis. Certain connective tissue tumors, such as angioendotheliosarcoma and myosarcoma, are apt to be of long duration and polypoid

in nature, and for many months they may simulate adenoma. A careful and complete study of the patient, particularly with tomographic studies, will usually disclose the invasive nature of these tumors. Adequate biopsies containing characteristic patterns usually make the diagnosis certain. Bronchoscopic biopsy material from small-celled carcinoma and angioendothelioma has proved difficult to differentiate from adenoma. Exploratory thoracotomy should not be delayed too long when the diagnosis of adenoma cannot be substantiated completely.

Benign bronchial tumors other than adenoma are much less common than was previously thought. Fibromas occur only about one-tenth as frequently as adenomas, and the characteristic patterns of adenomas are usually lacking in these. Ecchondromas, myomas and lipomas are also rare and have a characteristic histology.

Bronchiectasis is not always of the fetid type, with marked cough and sputum. The hemorrhagic type of bronchiectasis may simulate the clinical picture of adenoma. When bronchiectasis has been demonstrated and hemorrhage is the chief symptom, the presence of a concomitant adenoma should be kept in mind. In such cases bronchoscopic visualization and biopsy of the adenoma may be difficult. Tomographic studies may be of help.

There are three types of treatment for bronchial adenomas: local treatment, radiation, and pulmonary resection.

The local treatment may be accomplished endoscopically or by local resection through a transpleural approach. The endoscopic treatment is, we believe, less commonly indicated than it was formerly thought to be, because of (1) local recurrences; (2) danger of fatal complications; (3) inability to remove adequate amounts of the tumor; and (4) disabling symptoms from the distal suppurating lung still remaining. It must be admitted, however, that where adequate bronchial drainage can be re-established by removal of the endobronchial tumor, improvement is often satisfactory; and, even though late recurrences result, the general condition of these patients may remain good for as long as twelve years. Yet even these patients eventually change from a problem of bronchoscopic therapy to one of pulmonary resection. In preparation for pulmonary resection, re-establishment of bronchial drainage by endoscopic removal of the obstructing tumor should be performed whenever it is easily accomplished. But when these attempts are complicated by serious hemorrhage, failure to establish bronchial drainage easily, or the presence of persistent obstructing tumor, then bronchoscopic treatment should be abandoned in favor of pulmonary resection.

The number of patients operated upon by the transpleural approach, with local resection of the tumor, is still quite small. This method appears to be applicable to those tumors in which the distal lung has not yet been damaged permanently, in which the size is small, and in which dissection is easy.

Radiation therapy probably has little effect upon the tumor per se. Where distal infection is pronounced and bronchial obstruction complete, external radiation may produce an exacerbation of the symptoms. It is our feeling that those patients who had radiation therapy continued to live, not because of the therapy, but rather in spite of it. In our hands, intrabronchial radiation therapy has proved too cumbersome and the indications too indefinite.

Pulmonary resection appears the ultimate fate awaiting most patients with bronchial adenoma.[50, 51] This is so not only because of the persistence of the tumor itself, but also because of the continued presence of distal pulmonary suppuration. In our series, six, or one-third, of our cases have had pulmonary resection performed. Three of these underwent pneumonectomies and three lobectomies. There was one operative mortality. In all of these cases the tumor could never have been removed satisfactorily endoscopically because it was too large or too vascular, because it had thinned out the bronchial wall, because it had extended extrabronchially, or because it was inaccessible through the bronchoscope. In addition, the lung was either destroyed by pressure atrophy or bronchiectasis, and pulmonary suppuration was far advanced. Besides these six cases, there are seven patients whose cases we are still following. They have residual tumor, but the symptoms are not disabling after either deep external x-ray radiation or bronchoscopic removal. These patients have a future frought with a serious complication.

CONCLUSIONS

Bronchial adenomas are epithelial polypoid tumors which exhibit growth potentialities midway between distantly metastasizing carcinomatous and purely local polypoid bronchial tumors.

Bronchial adenomas have a characteristic clinical course which is related to their location in a large bronchus, their vascularity, and their slow growth.

Pulmonary suppuration distal to the bronchial obstruction, and not the tumor per se, is the chief cause of death.

Three morphologic types of adenomas occur: endobronchial, intramural, and extra-endobronchial. The incidence of the intramural and extrabronchial types is greater than previously reported.

Bronchial adenomas have been mistaken frequently for carcinoma, even after bronchoscopic examination, with biopsy, as well as for pulmonary tuberculosis despite careful clinical, but without bronchoscopic, examination.

The bronchoscopic appearance is most important in making the diagnosis of a polypoid bronchial tumor, but this alone will not always differentiate adenoma from the other polypoid tumors.

Histologic examination of bronchoscopic biopsy will definitely establish the diagnosis only when characteristic patterns are present.

Tomography offers a procedure which can determine the location, extent, and morphology of these tumors.

Endoscopic removal of bronchial adenomas is indicated in the endobronchial type to re-establish bronchial drainage.

Sooner or later, because of the growth of the extrabronchial portion or suppuration in the distal lung, pulmonary resection is indicated.

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DISCUSSION

DR. CAMERON HAIGHT, Ann Arbor.—The presentation of Dr. Stephens and Dr. Goldman, which you have just heard, is a most timely one, especially because of the fact that our knowledge of adenomas is still in its infancy. We have been very fortunate, I feel, in being able to see the wealth of material that has been so beautifully presented by Dr. Goldman. We have been interested, likewise, in the problem of bronchial adenomas, and I would like, with your permission, to present for your consideration and opinion a type of tumor which has been of interest to us. This tumor is a glandular type of neoplasm, examples of which were included by Jackson and Konzelmann in their article on bronchial adenoma. The case that I would like to present was at first considered by us as a bronchial adenoma, but the subsequent studies of the case lead us to believe that the tumor is in reality a low-grade carcinoma of the so-called salivary gland type. It is because of the interest in the differential diagnosis between this lesion and the strictly bronchial adenomas that I think this case might well be considered at this time.

The patient was a young colored girl 17 years of age, whose apparent age was only about 12 or 13. The symptoms had been of one year's duration and consisted of cough and occasional streaking of the sputum but no gross hemoptysis and no evidence of suppuration within the lung.

On admission, the x-rays showed a cystic bronchiectasis of the left lung. The bronchograms revealed a polypoid type of tumor extending into the left stem bronchus. The rounded nature of the tumor that was growing up into the left stem bronchus was readily seen. It completely obstructed the bronchus, allowing no ingress and egress of air. A biopsy specimen was reported as a low-grade carcinoma. Several aspects of the case, however, suggested that it was probably an adenoma; one was the age of the patient, 17; the second was the sex of the patient; and the third was the fact that the lesion had such a smooth nonulcerated surface.

We believed that a total pneumonectomy was indicated because the lesion was apparently too extensive to be removed by local bronchoscopic extirpation and because of the cystic bronchiectasis. Accordingly, two years ago a total pneumonectomy by the dissection technique was carried out and the patient's convalescence was entirely uneventful. At the time of the operation the tumor was seen to be very fragile, and as the bronchus was sectioned, a portion of the tumor immediately fell out of the peripheral part of the bronchial stump which had not been clamped.

The gross pathologic specimen disclosed a lesion which infiltrated the bronchial wall. A section made through the upper lobe bronchus at about 1 cm. from the upper lobe orifice showed the tumor mass extending into the wall of the upper lobe bronchus. The tumor also infiltrated the lung to a certain extent.

A photograph shows the small stature of the patient at the time of the operation. It is of interest that this type of tumor has occurred in a patient of this age. The recent photograph shows the development of the patient following operation. Although she is still quite small in stature, she apparently has had no embarrassment as the result of the operation.

This type of tumor should be clearly differentiated from the distinct adenomas which Dr. Goldman has presented. Dr. Maier, when he was with us, reviewed the literature of adenomas and has made a special study of the microscopic aspects of bronchial adenomas. I think you would be interested if he would present for us the microscopic appearance of this tumor and discuss in detail the histopathology of this type of lesion.

DR. HERBERT MAIER, New York.—Dr. Stephens and Dr. Goldman have shown us the histology of the typical endobronchial adenoma. In Dr. Haight's case the pathologic findings are somewhat different, although bronchoscopically the appearance of this tumor was similar to that of other adenomas. The tumor was covered by intact, stratified squamous epithelium, but otherwise the histopathology is different from the ordinary type of bronchial adenoma. A section taken through a portion of bronchial cartilage showed tumor on both sides of the cartilage. This is sometimes true in the type of adenoma that Dr. Stephens and Dr. Goldman have shown. In Dr. Haight's case, however, there was some extension of the tumor tissue into the cartilage itself. This tumor had an endobronchial portion and, in addition, a considerable extension into the wall of the bronchus, completely encircling it. In a section taken at some distance from the endobronchial portion of the tumor there were scattered areas of tumor tissue around the cartilage and among the normal bronchial glands. There was no capsule and there was considerable tendency toward infiltration. The arrangement of the tumor cells showed a striking resemblance to the appearance of mucous glands. The cells had a somewhat different appearance than in the typical adenoma and were arranged

in definite glandular formation, with considerable mucus present. One feature of the pathology of Dr. Haight's case that seems to me to be of considerable significance is that one section showed very definite infiltration of a nerve sheath by tumor tissue, which is considered a rather definite criterion of malignancy. Whether this tumor would metastasize, I think we cannot say definitely. Certainly the clinical appearance strongly suggested that the tumor had been present for a long time. Two similar cases have been observed by Dr. Jackson and Dr. Konzelmann and were included in an article on bronchial adenomas published several years ago. In a recent personal communication from Dr. C. L. Jackson, he tells me that one of the patients subsequently died, but no autopsy was obtained. So we do not know in that case whether there were any metastases present.

Dr. Brock, in a discussion of adenomas, has mentioned some cases in which the tumor bulged between the bronchial cartilages and produced a ripple-like effect on the bronchogram. He also pointed out the fact that there are atypical types of adenoma. Certainly, the best way in which we will get more information on this subject is by the group type of study that Dr. Brunn has suggested.

DR. STEPHENS.—Too much credit cannot be given to Dr. Goldman for his excellent presentation of this subject. Full credit is due him. It has been through his ferreting out of these cases that we have learned to become better acquainted with adenoma of the lung. Certainly, these patients have been treated for a great many different diseases before the true diagnosis has been arrived at. As Dr. Goldman said, a great proportion of these patients have been confined to tuberculosis sanatoria before they came to bronchoscopy.

Heavy doses of deep roentgen treatments have not affected the adenoma per se in our experience. We have noted some clinical improvement in our patients following deep therapy treatments, but certainly no change in the appearance of the adenoma either bronchoscopically or roentgenologically.

We have learned that it is important to reduce parenchymal infection in the lung distal to the obstructing adenoma before any major intrathoracic surgery is attempted. This can be accomplished by frequent bronchoscopic aspirations and the use of a small rubber catheter directed beyond the adenoma.

We still need better instruments to remove the intrabronchial portion of the tumor. Dr. Paul Samson of Oakland, Calif., has already accomplished considerable in this direction. Dr. Samson has designed a small high-frequency cautery for bronchoscopic use which has proved to be the most satisfactory instrument we have to remove the adenoma. Since bronchial adenomas are usually very vascular, their removal is frequently most difficult because of the severe bleeding that occurs upon the slightest trauma to the tumor. We feel it might be advisable in an early case to employ thoracotomy, going in and opening up the bronchus and, if the tumor is strictly limited to the endobronchial part, removing it and closing the bronchus. If the tumor has invaded beyond the bronchus, we believe the dissection of the vessels and the lymph nodes is necessary along with the removal of the involved lobe or lobes.

DR. PAUL C. SAMSON, Oakland, Calif.—I want to add my word of congratulation to Dr. Goldman for his presentation. Ever since he has been in San Francisco and we have had our meetings in San Francisco, we have talked about these things. I think the California Clinic must have an adenoma magnet. I have tried myself to find some on and have not succeeded in doing it. Again, I think it is important to follow out the idea of a tumor registry. This, I think, is a very good example of what we may gain by such a procedure, because if we

can prove that these tumors are locally invasive only, particularly when they are in the lower lobe, lobectomy should suffice rather than pneumonectomy. I think everyone agrees that if a carcinoma is visible through the bronchoscope, the entire lung should be removed rather than just the lobe.

Speaking of bronchial cauterization, I have been interested in this from the point of view particularly of treating tuberculosis lesions. I must confess that to date, I do not have an instrument with which I am wholly satisfied, although I hope to have one in the near future. The main trouble has been in producing a rod which is small enough in diameter so that one can easily see around it and at the same time have it perfectly insulated for the high-frequency current which comes through either the Bovie or Rose type of machine. If we use a rubber coating, the type of instrument that we obtain is too large to be used successfully except through a very large bronchoscope. We have been working with various types of high dielectric varnishes and lacquers and I hope we will have something which will help solve the problem of intrabronchial removal of this type of tumor.

DR. HAROLD NEUHOF, New York.—Like others I have enjoyed the scholarly presentation of Dr. Stephens and Dr. Goldman. I believe that attention was first called to the subject of benign tumors of the bronchus, generally termed bronchial adenoma, by Dr. Wessler and Dr. Rabin of the Mount Sinai Hospital. Since their first report there must have been at least thirty cases under observation and treatment at that institution. The reason I am joining in the discussion is to refer briefly to the experience at Mount Sinai Hospital, which has been in a general sort of way, different from that reported here. The difference to which I refer is concerned with the question of treatment. The great majority of our cases have not required the major surgical operative procedures which have been suggested as a form of treatment for benign bronchial tumors. At the moment I can recall very few instances in which bronchoscopic removal of the growth was not essentially adequate for the relief of symptoms. By that I do not mean that all patients were cured by bronchoscopic removal of the growth, but I do mean that clinical manifestations were sufficiently eliminated in the great majority of instances so that patients remained well or practically well for an indefinite period of time. In instances in which there has been infection distal to an occluding tumor, the excision of the neoplasm via the bronchoscope usually has been sufficient to supply the drainage required for the continuance of at least a tolerable existence. To the best of my knowledge, most of the patients are essentially well, although some require repeated bronchoscopic treatments. These statements do not imply that I am of the opinion that no patient should be subjected to a major operative procedure such as lobectomy or pneumonectomy. It does mean, however, that treatment by a skilled bronchoscopist, with the effort to remove most or all of the tumor in one or more stages, usually should be resorted to before having recourse to lobectomy or pneumonectomy. It should always be borne in mind that we are dealing with a nonmalignant tumor and, therefore, that complete removal is not the primary objective.

Attention should be called also to the fact that upon occasion the microscopic findings of bronchoscopic specimens may vary in the same patient, depending upon the time at which they are taken and the site of removal. Thus I recall the mother of a physician in whom the first bronchoscopic biopsy was performed some fifteen years ago. From that time over a period of years portions of the tumor were removed at various sittings for the purpose of establishing drainage beyond the more or less occluding tumor. One microscopic specimen would be characteristic of adenoma, another one would not, and upon one examination, the diagnosis of carcinoma was made. This patient died not from the bronchial lesion, but

from cerebral arteriosclerosis. At autopsy the tumor of the bronchus was found to be nonmalignant. Reference should be made to the difficulty in differentiating microscopically between some of the tumors of the bronchus under discussion and carcinoma. Even experienced pathologists encounter great difficulty at times, and render reports subsequently found to be erroneous. One recalls the brilliant result reported by Churchill at Ann Arbor in 1932 in which the right middle and lower lobes were successfully removed for a bronchial tumor thought to be malignant. Subsequently, Churchill reported that the pathologist revised the diagnosis. When it is realized that errors may be made in the microscopic diagnosis when the whole tumor can be examined, the margin of error in the examination of fragments removed through the bronchoscope may of course be far greater. In my opinion, the correct diagnosis of a nonmalignant bronchial tumor can usually be based on the age of the patient, the history of the case, and the gross features of the neoplasm as observed through the bronchoscope. According to observations made at Mount Sinai Hospital bronchoscopic removal of the tumor suffices for the control of the clinical manifestations, at any rate, in the great majority of cases.

DR. CLARENCE CRAFOORD, Stockholm.—I want to add my congratulations to Dr. Goldman and Dr. Stephens for their excellent paper. I believe, however, that we ought to be very careful in drawing definite conclusions on such a comparatively small series of cases as is presented. It is hard for me to understand why these benign adenomas could not become malignant as benign tumors do in other regions of the body.

We have had one case very similar to the one that Dr. Haight presented. In that case there was one part of the tumor growing inside the bronchus very well encapsulated; another part of it was growing outside of the bronchial wall, directly infiltrating the pericardium. In that case there was also metastasis in the lymph nodes in the pulmonary hilum. It must have been of very low grade malignancy. We did a radical operation which included partial resection of the pericardium. It is now about four years since the operation and there has been no evidence of metastasis of the tumor.

DR. I. A. BIGGER, Richmond.—I was very much interested in Dr. Stephens' remarks in regard to the possibility of removing some adenomas by bronchotomy. It has seemed to me for several years that in certain well-selected cases of bronchial adenoma, where the diagnosis is well established by biopsy and where lung damage was not too advanced, it might be desirable to remove the adenoma by bronchotomy, with preservation of the lung. Of course, where there is far-advanced damage to the lung, I think pneumonectomy or lobectomy, whichever is indicated, is the treatment of choice.

In 1932, I had occasion to perform a bronchotomy on a patient with an adenoma which was in almost the identical location as the one shown by Dr. Haight this morning. We found the tumor was quite easily removed by a posterior approach, incising the bronchus longitudinally in the portion in which there was no cartilage. The pathologist later made a diagnosis of carcinoma, so we did a pneumonectomy. The patient, unfortunately, had an infection in the pleura as the result of the rupture of a superficial abscess and after operation developed a pericarditis from which he died six weeks later. We have never been certain whether the tumor was carcinoma or adenoma, although we have had the slides checked by several competent pathologists. Clinically the tumor was well circumscribed and therefore was probably an adenoma. In this particular case there was such extensive lung damage that pneumonectomy would have been necessary eventually.

DR. W. A. HUDSON, Detroit.—A few years ago at the meeting of the Thoracic Surgeons and at a later meeting of the Bronchoscopic Society I reported an instance of a patient who had been seen in a number of clinics, with an unexplained complaint of bleeding. He had been bronchoscoped at two of these clinics, without a diagnosis being made. Fortunately, or unfortunately for me, when I bronchoscoped him I was able to identify a small pedunculated mass projecting from the orifice of a secondary division of the left lower lobe bronchus. X-ray findings had previously given no intimation as to where the disturbance would be located. This mass was removed in toto and a diagnosis of adenocarcinoma was given to me by the pathologist. It is now twelve years since the mass was removed and the patient has had no recurrence of symptoms and is continuing in his business. There is apparently no question but what this was a very benign type of growth.

In Dr. Goldman's presentation he very accurately illustrated the three different positions that the growth may assume and I think this is a very important factor to be taken into consideration in estimating the possibilities from the standpoint of treatment. I can well understand how one would justify very simple and very conservative procedures for the removal of a pedunculated mass that can be removed in toto without the production of additional damage or narrowing of the bronchus, as in the one instance of which he showed the diagram.* On the other hand, a mass of the type that has a collar button effect, one large portion outside the bronchus invading the lung tissue and a smaller portion projecting between the cartilages into the bronchus and obstructing the bronchus, would be unsuitable for bronchoscopic removal, and I think it would be foolhardy to offer a patient with that type of tumor the advantage, or disadvantage I should say, of bronchoscopic attempts at removal. There is danger of local injury, and if one were fortunate enough to remove the mass, the chances of complications from the mechanical factors that are involved either at the time of the operation or the follow-up strictures that would develop at the site of the operation are too great to warrant one's risking such a procedure.

The third type of tumor that Dr. Goldman has illustrated, which may still be of a more or less benign character but located entirely outside the bronchus, is certainly not suitable for bronchoscopic removal. I believe that bronchoscopy does offer a means of removal for a pedunculated mass at the time of diagnosis, or that follow-up bronchoscopy may be performed, and if the microscopic sections obtained warrant the consideration that it is a benign type of tumor, one may then be justified in proceeding along the very conservative lines that have been mentioned. But, if at the time of the bronchoscopy and subsequent studies it is found that there is evidence of the mass projecting beyond the bronchial wall, or that there is definite fixation in that bronchial wall suggesting invasion of the adjacent tissue, I do not believe that we are justified in depending upon bronchoscopic removal to give an ultimate cure. I am thinking, not in terms of the stoppage of the growth, but also of the permanent benefit to the patient's health that would not be obtained if he developed strictures and other complicating factors that would keep him in a state of invalidism. In that event, if the diagnosis is suggestive of a benign tumor, I would certainly prefer an excision of that portion of the lung, and lobectomy might be considered.

In regard to the use of a cautery loop for the removal of these tumors, I have on certain occasions used such a loop for the tunneling and re-establishment of a canal in carcinomatous obstruction of the esophagus, where the patient had complete obstruction and inability to obtain fluids and where it seemed undesirable to undertake to feed the patient by gastrostomy; and in such cases I have had the satisfaction of re-establishing a canal by the use of the loop.

DR. GOLDMAN.—I fully agree with Dr. Hudson that it is foolhardy to attempt the removal of a large extrabronchial tumor by bronchoscopy. If the tumor does not approximate very closely the mucous membrane and the fibrous capsule, it may be dangerous even to take a deep biopsy, although such procedure would be necessary to obtain characteristic patterns. We have a patient with a very large extrabronchial mass who is ill with a high fever following the taking of a biopsy.

I also fully concur with Dr. Hudson's remarks about local removal. Likewise, partly corroborating Dr. Neuhof's discussion, I agree that local removal of the tumor to the point of opening the bronchus and re-establishing bronchial drainage is often sufficient to keep these patients in good health; and that, so far as we can judge, removal of the endobronchial portion of the tumor does not tend to produce metastases. None have been observed in our patients. Perhaps Dr. Crafoord may be correct in saying that, as we go on, we shall observe that these tumors will become larger and possibly will even metastasize.

Dr. Stephens said the other day that there is no good way to determine the extent of the extrabronchial tumor, but perhaps the use of planography may permit this.

I wish to thank Dr. Haight and Dr. Maier for their discussions. I believe that they are right in saying that the case of tumor they presented may represent something different from the adenomas we described. We have not been fortunate enough to have a case exactly like theirs.

On Dr. Neuhof's service bronchial adenomas constitute some 6 per cent of all bronchial tumors; on Dr. Churchill's service at the Massachusetts General Hospital, they make up 10 per cent of all bronchial tumors and 25 per cent of resectable pulmonary tumors. It is evident from these figures that bronchial adenomas form an important group and that no discussion of bronchial carcinoma can be complete without a consideration of adenomas and their separation from carcinomas. The importance of leaving distal suppuration untreated was clearly shown in Dr. Haight's presentation. It seems probable to me that, in the future, lobectomies and pneumonectomies will be performed more often because of residual symptoms arising from permanent damage to the lung or for cystic bronchiectasis, than because of the adenomas.

Regarding Dr. Crafoord's case, there is a good deal in the literature now to indicate that these tumors may be of a nature similar to the carcinoids of the gastrointestinal tract that were so thoroughly investigated by Masson. If it can be proved that the bronchial adenomas are of the same type, we can expect metastases later in these adenomas—even later, perhaps, than has been observed so far. I believe, however, that metastasis in bronchial adenoma must be rare, if it does occur. I agree with Dr. Bigger that the future will see new surgical procedures applied to these tumors.

A STUDY OF 300 CASES OF ACUTE EMPYEMA THORACIS (132 STREPTOCOCCIC AND 168 PNEUMOCOCCIC)

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ALTHOUGH the ancients even before Hippocrates[1] had recognized empyema thoracis, it was not until the middle of the nineteenth century that a deliberate attempt was made to treat acute empyema. Roe,[2] in a paper delivered before the Royal Medical and Chirurgical Society of London in 1844, advocated aspiration as a therapeutic measure. He reported nine cases treated in this manner, with eight recoveries and one fatality. Fifteen years later Goodfellow and DeMorgan[3] introduced intercostal drainage as another method to evacuate the pus from an acute empyema thoracis. In 1860 Walter[4] resected a sound rib to drain an empyema of sixteen months' duration. Roser[5] suggested rib resection in the drainage of postpneumonic empyema, but it was not until 1865 that he employed it. Weissenborn[6] in 1876 reported five cases of empyema treated by rib resection drainage. Until the early part of the twentieth century, the latter method was in common practice.

The cases of empyema encountered during the influenzal (*Streptococcus hemolyticus*) pandemic of 1918 confronted the surgeon with conditions which had no counterpart in past experience. In civil practice most of the cases of empyema had been postpneumonic and were drained after the acute pneumonic process had subsided. In the influenzal epidemic, however, the empyema developed during the pneumonia, and in many instances drainage was instituted during the acute phase of the pneumonia. Modern warfare and the pandemic produced a situation the like of which had not been encountered previously. During the Great War, in many military camps, drainage was instituted in accordance with the experiences of civil practice. The unusually high mortality which followed in the wake of this procedure led to the appointment of an Empyema Commission whose responsibility it was to investigate the causes of death in influenzal empyema. The contributions of this Commission[7] and the subsequent work of Graham[8] and his co-worker Bell[9] have become milestones in surgery. Briefly, these investigators showed that neither the lung nor the mediastinum was stabilized during the early stages of a streptococcic empyema and that an open pneumothorax at this time caused a displacement of the mediastinal structures into the contralateral hemithorax, with functional embarrassment to the opposite lung. They were then able to

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explain the patient's asphyxial death on the basis of the increased anoxemia which followed an open pneumothorax before the mediastinum was fixed. They therefore advocated that empyema should not be drained until the mediastinum is fixed and the acute phase of the pneumonia has subsided. The adherence to this principle during the war and later in civil practice markedly reduced the mortality in empyema. The morbidity, however, still remains high. In recent years literally hundreds of methods have been introduced which attempt to decrease this morbidity. Their very number attests to the fact that no one procedure can be relied upon in the management of all cases of empyema.

Various statistics have been cited to prove that empyema in children under 2 years of age carries with it a high mortality. The reports of Brown,[10] Hochberg and Kramer,[11] Paschlau and Lehmann,[12] Spence,[13] Steinke,[14] Wilensky,[15] and others would tend to corroborate this view.

TABLE I

	MORTALITY IN FIRST YEAR OF LIFE (%)	MORTALITY IN SECOND YEAR OF LIFE (%)
Brown	41	43
Hochberg and Kramer	54	50
Paschlau and Lehmann	56-74	24-59
Spence	66	51
Steinke	71	45
Wilensky	48	31

Similarly, Michalowicz,[16] in a review of 1,450 cases of empyema in children in four hospitals in Poland, noted that the mortality curve reaches its maximum during the first six months of life and remains high until the third year, when it begins to decrease. It must be pointed out, however, that these statistical studies are made without regard for the etiological cause, the etiological organism, or the complications present at the time therapy was instituted.

In a previous communication[11] it was shown that the mortality in empyema per se in children is not high and that the mortality varies with the severity of the complications and the virulence of the etiological organism. In this communication the writer will show that empyema is more commonly associated with secondary complications in the child than in the adult, and that regardless of the age of the patient, the mortality is related to the severity of the complications; and further, that the morbidity is dependent upon the adequacy of drainage. To this end, a review of 132 streptococcic and 168 pneumococcic empyemas was undertaken from the following points of view:

1. Age of the patient
2. Etiological organism of the empyema.

3. Duration of the preceding illness and of the empyema before the latter was diagnosed and before surgery was instituted.
4. Method of treatment.
5. Complications present at the time therapy was instituted.
6. Other preoperative complications which might influence the outcome of the case.

The cases for this study were taken from the case records of the Jewish Hospital of Brooklyn for patients admitted between 1929 and 1936. All patients included in this series had preoperative diagnostic thoracentesis, with bacteriologic and cytologic studies of the fluid thus obtained. The mere presence of bacteria in a serous, serofibrinous, or serohemorrhagic fluid did not constitute sufficient evidence to warrant the diagnosis of empyema. It has been pointed out (Graham) that bacteria may be present in pleural effusion which accompanies a pneumonia without that patient's subsequently developing an empyema. The criteria for the diagnosis of empyema was the presence of frank pus in the pleural cavity. The criteria for cure of empyema was (1) an afebrile state, (2) minimal drainage, (3) complete expansion of the lung, and (4) roentgenographic evidence of complete expansion of the lung without retention of pleural fluid. Conversely, those cases were considered surgical failures in which (1) there was a febrile course, (2) drainage persisted, (3) the lung was incompletely expanded, (4) the roentgenograms showed retained fluid or incomplete expansion of the lung, and (5) the patient required over ninety days of postoperative hospitalization without conforming to the above criteria for cure.

STREPTOCOCCIC EMPYEMA

In the 132 cases of streptococcic empyema there were eight which failed to respond to surgical drainage. In the remaining 124 cases empyema was diagnosed in thirty-eight instances before the tenth day of illness; in twenty-three cases it was diagnosed between the eleventh and fourteenth days of illness, and in the remaining sixty-three cases, after the fourteenth day of illness. Regarding the latter group of cases, it must be added that thirty-one cases were admitted to the hospital after a fortnight of illness and were subjected to surgical drainage within twenty-four hours after admission.

Fig. 1 represents thirty-one cases of streptococcic empyema which were treated by aspiration; ten of these cases were uncomplicated and twenty-one were complicated. In addition, there were ten patients (six complicated cases and four uncomplicated) who failed to respond to aspiration and later required another form of drainage. There were, therefore, four d aths (29 per cent*) in the uncomplicated

*Throughout this paper fractional percentages have been omitted and have been replaced by the whole number closest to the true figure.

cases and twenty deaths (74 per cent) in the complicated cases. The complications noted in the twenty-one cases shown in Fig. 1 are given in Table II.

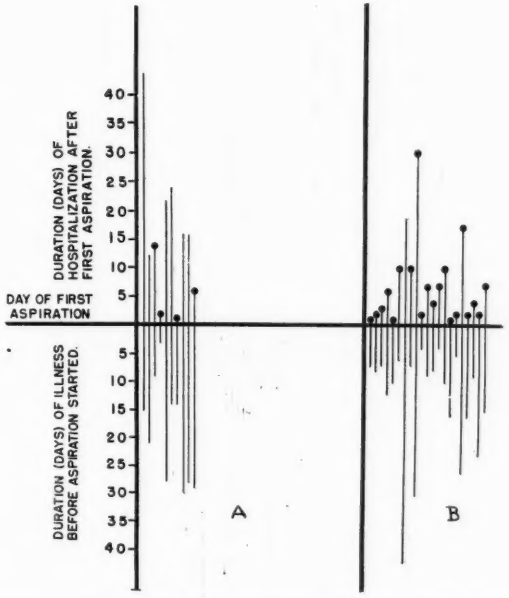

Fig. 1.—Thirty-one cases of streptococcic empyema which were treated by aspiration. *A*, Ten uncomplicated cases with four fatalities; *B*, twenty-one complicated cases, with twenty fatalities. The solid dot indicates the day of death.

TABLE II

COMPLICATION*	NUMBER	DEATHS
Bilateral bronchopneumonia	5	5
Bilateral bronchopneumonia and empyema	2	2
Bilateral bronchopneumonia and peritonitis	2	2
Pericarditis and pneumonia	2	2
Pericarditis and lung abscess	2	2
Multiple lung abscesses	2	2
Bilateral lobar pneumonia and empyema	1	1
Pericarditis and gangrenous bronchitis	1	1
Brain abscess	1	1
Erysipelas	1	1
Pleurobronchial fistula	1	1
Empyema necessitatis	1	

*The complications refer to "clinical complications" and not those seen at necropsy. In many instances more than one complication was present, but only those are listed which appeared to play the most important role in the patient's subsequent course.

Fig. 2 represents thirty-five cases treated by closed intercostal drainage. In this group there were twenty-seven uncomplicated cases, with five fatalities, and eight complicated cases, with seven fatalities. In ad-

dition, there were four uncomplicated and two complicated cases of empyema which failed to respond to this form of drainage. On the basis of total number of cases treated in this group, the mortality in

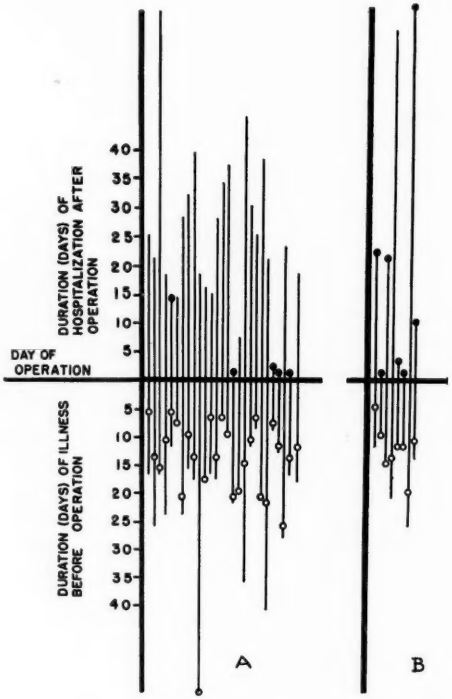

Fig. 2.—Thirty-five cases of streptococcic empyema which were treated by intercostal drainage. Twenty-seven cases were uncomplicated, and eight were complicated.

In this and the following graphs the small circle indicates the day of the illness on which empyema was diagnosed; the solid dot denotes the day of the patient's death after the beginning of the treatment of the empyema. Each vertical line represents the course of one patient's illness. Each series is arranged according to age, the youngest subject being first and the oldest last. *A* represents the uncomplicated cases of empyema and *B* represents the complicated cases.

TABLE III

COMPLICATION	NUMBER	DEATHS
Ruptured lung abscess and pleurobronchial fistula	2	1
Pleurobronchial fistula	2	2
Bilateral pneumonia and empyema	1	1
Pericarditis and pneumonia	1	1
Pleurobronchial fistula, pericarditis, and pneumonia	1	1
Bronchopneumonia and lung abscess	1	1

the uncomplicated cases was 16 per cent, whereas in the complicated cases it was 70 per cent. The complications in the above eight cases are shown in Table III.

Fig. 3 represents fifty-eight cases of streptococcic empyema which were treated by rib resection drainage. Forty-three of these cases were uncomplicated and fifteen were complicated. In addition, there were five uncomplicated cases and three complicated cases which

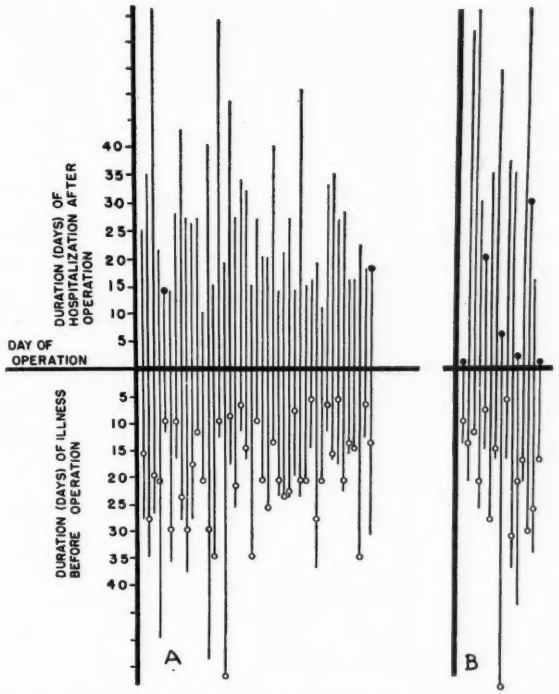

Fig. 3.—Fifty-eight cases of streptococcic empyema which were treated by rib resection drainage. There were forty-three uncomplicated cases and fifteen complicated cases.

TABLE IV

COMPLICATION	NUMBER	DEATHS
Lung abscess	3	1
Bilateral bronchopneumonia	2	2
Pericarditis and bronchopneumonia	2	1
Pericarditis	2	1
Bilateral bronchopneumonia and empyema	2	1
Empyema necessitatis	2	
Spontaneous pneumothorax	1	
Ruptured peripheral lung abscess	1	

were surgical failures. On the basis of the total number of cases treated in these two groups, the mortality in the uncomplicated cases was two (4 per cent) in forty-eight cases, and six (33 per cent) in eighteen complicated cases. The complications in the fifteen cases noted on the accompanying graph are given in Table IV.

COMMENT

A review of 132 cases of streptococcic empyema is presented. Thirty-one were treated by aspiration, thirty-five by intercostal drainage, and fifty-eight by means of rib resection drainage. In addition, there were eight cases treated by the latter method which were surgical failures. Each method presented some failures. By aspiration alone there were ten (24 per cent); by intercostal drainage there were six (15 per cent); and by rib resection drainage there were eight (13 per cent). The mortalities in each group of cases were directly proportional to the number of cases in which the empyema was complicated. That the mortality was influenced by the number and severity of the complications rather than by the empyema itself is readily shown in Table V.

TABLE V

	NUMBER	PERCENTAGE
Total number of cases	124	
Total mortality	44	36
Total number of complicated cases	44	36
Mortality in the complicated cases	33	75
Mortality in the uncomplicated cases	11	14

Thus, the mortality in the complicated cases of streptococcic empyema was more than five times as great as that in the uncomplicated cases. Considering the percentage of mortality and the percentage of failures by aspiration, intercostal drainage, and rib resection drainage, we note that the best method for draining a streptococcic empyema would be via a rib resection. However, one must be cognizant of the fact that the cases in this series were treated in accordance with the principles of Graham and Bell. In further conformity with these principles and in those instances in which there was toxicity and/or cardiorespiratory embarrassment, repeated aspiration was performed until the pneumonia had subsided and the fluid had become frankly purulent. Rib resection drainage therefore was deferred as long as it was thought prudent. In several instances intercostal subaqueous drainage was established because it was felt that the pneumonia was subsiding and the pus was not quite thick enough to permit a safe rib resection drainage. The objection to too frequent aspirations is that the chances of developing an empyema necessitatis or a subcutaneous infection becomes greatly enhanced with each aspiration of the pleural content. In addition, the removal of the fluid from the pleural cavity by aspiration is accomplished relatively rapidly. A closed intercostal drainage can be instituted early and regulated to remove the fluid slowly and continuously. In the presence of a perforated lung it will also act in such a manner as to deflate continuously the pleural cavity. The oft-repeated objection to inter-

costal drainage, i.e., leakage about the tube, may be obviated by the use of a collodion, rubber cement, or liquid adhesive dressing about the drainage tube at its entrance into the thoracic wall. Since the pus in streptococcic empyema is relatively thin until late in the course of the disease, the intercostal tube will often afford adequate means of drainage. In several instances in which closed intercostal subaqueous drainage was instituted during the acute pneumonic process and while the pus was still thin, it was noted that this sufficed to evacuate completely the pleural cavity and to permit complete re-expansion of the lung and cure of the empyema.

PNEUMOCOCCIC EMPYEMA

In the 168 cases of pneumococcic empyema under consideration, there were seven surgical failures. In the remaining 161 cases, empyema was diagnosed in thirty-six instances before the tenth day of illness, in seventy-six between the eleventh and fourteenth days of illness, and in the remaining forty-nine after the fourteenth day. Regarding the latter group of cases, it must be added that about two-thirds of these cases entered the hospital with empyema and were treated for the latter condition within twenty-four hours after entry.

Fig. 4 represents twenty-four cases of pneumococcic empyema treated by aspiration. There were eight uncomplicated cases, with three deaths, and sixteen complicated cases, with fifteen fatalities. In addition, there were sixteen uncomplicated cases treated by this method which later were subjected to another form of drainage. The mortality, therefore, was 13 per cent of the total number of uncomplicated cases and 94 per cent of the complicated cases. On the basis of the total number of uncomplicated cases treated by aspiration, there were 40 per cent failures. Table VI shows the complications in this group of cases.

TABLE VI

COMPLICATION	NUMBER	DEATHS
Bilateral bronchopneumonia	6	6
Contralateral bronchopneumonia	3	3
Pericarditis	2	2
Lung abscess	1	1
Multiple lung abscesses	1	1
Cellulitis of the chest wall	1	1
Bronchopleural fistula with lung abscess	1	1
Bronchopleural fistula	1	

Fig. 5 represents twenty-nine cases of pneumococcic empyema treated by closed intercostal drainage, of which number, twenty-seven were uncomplicated and two were complicated cases. In addition, there were twenty-two cases which later required rib resection drainage; sixteen of these cases were uncomplicated and six were complicated. In the un-

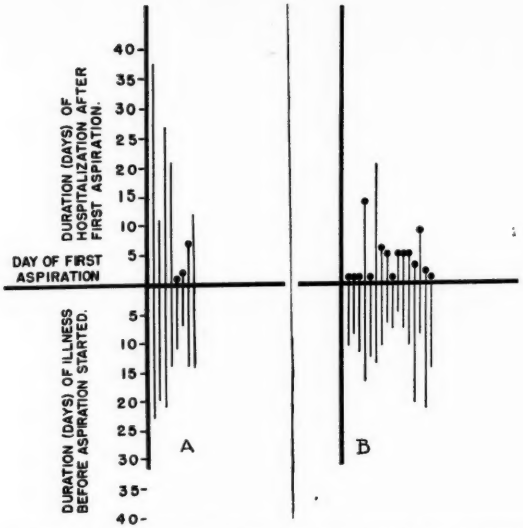

Fig. 4.—Twenty-four cases of pneumococcic empyema which were treated by aspiration. Eight were uncomplicated cases and sixteen were complicated.

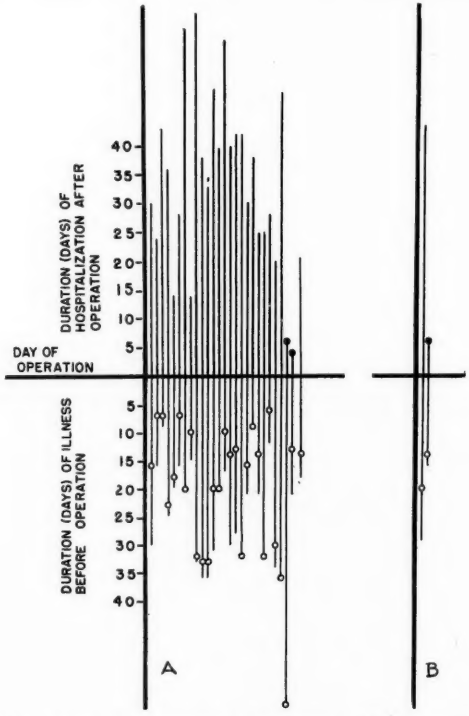

Fig. 5.—Twenty-nine cases of pneumococcic empyema which were treated by intercostal drainage. Twenty-seven were uncomplicated and two were complicated.

complicated cases there were two fatalities, and in the complicated cases there was one death. The incidence of failures was twenty-two in fifty-one cases, or 43 per cent. On the basis of the total number of uncomplicated cases treated by intercostal drainage, the mortality was two in forty-three cases, or 4 per cent, whereas in the complicated cases, it was one in eight cases, or 13 per cent. The complications in the above two cases are given in Table VII.

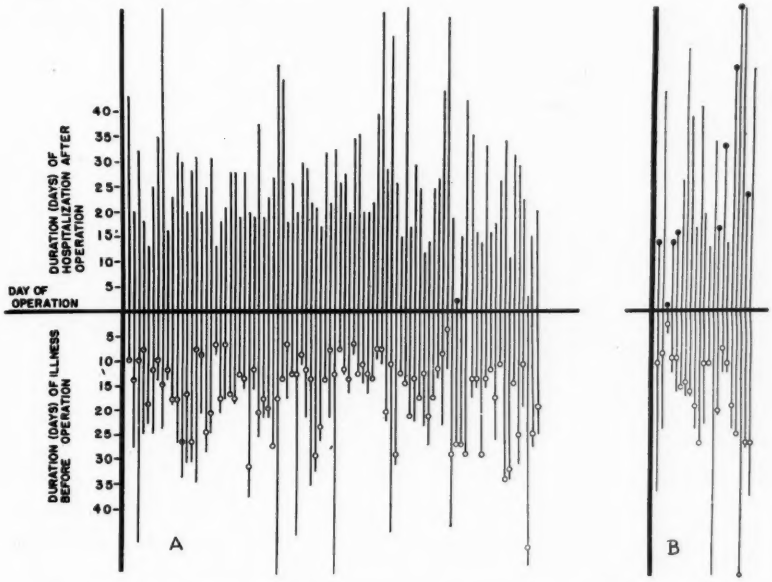

Fig. 6.—One hundred and eight cases of pneumococcic empyema which were treated by rib resection drainage. Eighty-seven were uncomplicated cases and twenty-one were complicated.

TABLE VII

COMPLICATION	NUMBER	DEATHS
Pleurobronchial fistula	1	
Lung abscess and pneumonia	1	1

Fig. 6 represents 108 cases of pneumococcic empyema treated by rib resection drainage, twenty-one of which were complicated and eighty-seven, uncomplicated. This group includes all those cases previously treated by aspiration and/or intercostal drainage. There was one fatality in the uncomplicated cases and nine fatalities in the complicated cases. In addition to the above 108 cases, there were seven (6 per cent) which failed to respond satisfactorily to this method of drainage. Four of these were uncomplicated and three were complicated cases. The mortality calculated on the basis of the total number of cases in this

group is, therefore, 1 per cent in the uncomplicated cases and 38 per cent in the complicated cases. The complications in the twenty-one cases are given in Table VIII.

TABLE VIII

COMPLICATION	NUMBER	DEATHS
Pleurobronchial fistula	4	1
Bilateral bronchopneumonia	3	2
Lung abscess	3	1
Contralateral bronchopneumonia	2	1
Multiple lung abscesses	2	
Pericarditis	2	1
Lung abscess, with contralateral pneumonia	1	1
Suppurative mediastinitis	1	1
Bilateral empyema	1	
Empyema necessitatis	1	
Peritonitis	1	1

COMMENT

The foregoing is a résumé of 168 cases of pneumococcic empyema, twenty-four of which were treated by aspiration, twenty-nine by intercostal drainage, and 108 by rib resection drainage. This series includes another seven cases which failed to respond to rib resection drainage. In this study it was noted that 40 per cent of the cases treated by aspiration failed to respond to that form of therapy. In those treated by intercostal drainage the percentage of failures was 43, and in those treated by rib resection drainage, the failures were 6 per cent. Furthermore, in each group of cases it was noted that the number of fatalities was directly proportional to the number of cases in which the empyema was complicated.

TABLE IX

	NUMBER	PERCENTAGE
Total number of cases	161	
Total number of complicated cases	39	24
Total mortality	31	19
Mortality in the complicated cases	25	64
Mortality in the uncomplicated cases	6	5

Thus, the mortality in cases of pneumococcic empyema is related to the incidence of complicated cases and not to the incidence of empyema per se. In considering the percentage of mortality and the failures of each of the methods discussed above, it will be noted that the best method to be employed in draining the uncomplicated pneumococcic empyemas is rib resection. However, it must be added that every case of pneumococcic empyema does not require immediate rib resection drainage. The basic principles enunciated by Graham and his co-workers, and previously referred to in the section on streptococcic empyema, are

equally applicable to the cases of pneumococcic empyema. If need be, aspiration may be performed until the pneumonia has subsided and the viscosity of the pus has increased. At this stage one may safely institute rib resection drainage. It does not seem to be in conformity with the principles of adequate drainage to expect thick, fibrinous, semi-organized coagulum to pass through an aspirating needle or even through the usual intercostal tube. Even in those of the cases in which intercostal drainage was successful, the greatest difficulty encountered was the management of the obstructing coagulum within the drainage tube.

DISCUSSION

The physical signs and roentgenographic findings suggesting an acute nontuberculous empyema are readily available in any standard text-book on the subject and therefore need not be entered into here. Suffice it to mention that in any case in which there is a history of a recent pneumonia, an elevated temperature, and percussion flatness of the thorax, the presumptive diagnosis should be empyema. The final diagnosis, however, rests upon the aspiration of pus from the pleural cavity. The importance of a diagnostic puncture cannot be overestimated. The gross appearance of the exudate will usually tell the physician whether the fluid is thick or thin, purulent or serous. Microscopic examination will confirm the presence or absence of pus cells and bacteria. Culture will tell which organism is responsible for the empyema and will aid in determining the prognosis and treatment.

Rienhoff and Davison,[17] in a study of eighty patients under 2 years of age, with empyema, noted that the diagnosis was not made until the time of necropsy in approximately 20 per cent of the cases. From the writer's observations of such cases at necropsy, it appears that had the diagnosis been made, no adequate therapy could have been instituted because of the poor condition of the patient and the other associated complications. In every instance in which necropsy was performed on a patient with undiagnosed empyema, there were present associated complications which were severe enough to cause the patient's death. Cameron[18] too has observed that where an autopsy was performed after empyema additional complications were always found. The incidental finding of empyema does not imply that had the diagnosis been made, the patient's life would have been spared. Empyema is seldom a surgical emergency and is still less often a surgical emergency during the acute phase of pneumonia. In the early stages of the disease empyema is best treated by supportive measures and neglect of direct attack of the empyema itself.

An examination of the methods advocated in the management of empyema from the time of Hippocrates[1] to the present day[19, 20] shows

that all procedures attempt to hasten the patient's recovery by stressing the importance of one or more of the following phases: (1) evacuation of the pus; (2) sterilization of the pleural cavity; (3) re-expansion of the lung; (4) obliteration of the pleural space; and (5) restitution of the thorax to integrity. It should be stated that no empyema can be considered cured until all five objectives have been attained. The problem which confronts the physician is not one of immediate cure, but of the greatest number of cures at the least expense of life and with the shortest period of debility. Whenever possible, the empyema should not be attacked surgically until other complications have been ruled out, or, if they are present, until they have subsided or are under control. Frequently, such complications assume greater importance to the life of the patient than does the empyema. The aim of the surgeon is to drain the pus of uncomplicated empyema as quickly and as adequately as the patient's condition will allow and to help restore the patient's health as soon as possible. Among the manifold methods devised to evacuate purulent collections from the pleural cavity, one discerns but three principle methods, namely, (1) aspiration, (2) intercostal drainage, and (3) rib resection drainage.

Aspiration should be employed as a diagnostic adjuvant or as a palliative treatment, although occasionally it may suffice to cure a localized collection of pus. Repeated aspiration, however, in the presence of a large empyema is neither sound surgically nor innocuous. A subcutaneous abscess may readily be produced, even when precautions are taken to prevent its occurrence. The resulting phlegmon of the chest wall starts deeply and may not be recognized until the process has advanced a considerable distance. The writer shares the opinion of Eggers,[21] who believes that there is a definite danger in the continuance of aspiration over a long period. Among the eighty-one patients treated by this method, there were forty-two fatalities and twenty-six instances in which it was unsuccessful. Such statistical results do not support the contention of the advocates of this method that aspiration can be relied upon to cure empyema thoracis. Lockwood[22] believes that in the early stages of the disease, if the patient is dyspneic and the fluid reaccumulates rapidly, aspiration may be performed even as often as every few hours, but he doubts its efficacy in curing empyema.

A closed intercostal drainage has many advantages over aspiration in that it requires but one entry into the pleural cavity and can be so arranged as to function as a continuous drainage system. The rapid or sudden release of pus which takes place during aspiration of an empyema (particularly in children) may produce pulmonary edema and further embarrass the patient's respiration. This, too, may be obviated by a simple closed intercostal drainage. In the ninety-two

cases in which this treatment was instituted, there were fifteen deaths and twenty-eight cases in which this method failed to drain adequately the pleural contents. The most striking and dramatic results of closed intercostal drainage were obtained in those cases in which the patient was acutely ill, in which there was cardiorespiratory embarrassment, and in which the pus was thin. The relief of some of the intrapleural tension caused by the massive effusion was often striking and lasting, and indeed, saved the life of more than one patient. If early surgical intervention is necessary owing to the rapid reaccumulation of pus or interference with cardiorespiratory function, the simplest method must be chosen which will give the maximum and longest relief as well as permit continuous drainage. During the acute pnuemonic process, regardless of whether the etiological organism is streptococcus or pneumococcus, this method may be employed safely. Domanig[23] believes that closed drainage is indicated in all acute nonputrid empyemas with total or extensive empyema cavities and in the presence of other severe diseases, especially those involving the thoracic organs. He particularly advises its use in children. In addition, such drainage may be instituted readily at the patient's bedside and does not require removal of the patient to the operating room. When the pus is no longer seropurulent or where there has been a delay in institution of drainage, this method is usually inadequate.

Of all the methods proposed, rib resection drainage appears to be the most serviceable in the treatment of empyema. Except in those cases in which it is definitely contraindicated, rib resection drainage ensures the best method of drainage, with no additional embarrassment to the patient. Among the 181 patients treated by this method, there were eighteen deaths and fifteen cases in which this method failed to give satisfactory results. In cases of early empyema, especially in the streptococcic form, rib resection drainage should be delayed until the pus becomes thick. The opening into the pleural cavity after rib resection is usually of such size that it increases the collapse of the affected lung. Such collapse, particularly during the pneumonia, will further decrease the patient's vital capacity and increase the anoxemia. On the other hand, in the cases of pneumococcic empyema it will afford ample means for drainage without embarrassing the patient's respiration. Once the acute pneumonic process has subsided and the drainage instituted previously has proved itself inadequate, then rib resection drainage should be instituted without further delay. In cases of streptococcic empyema it should be delayed until the pus becomes thick, whereas in cases of pneumococcic empyema rib resection drainage may be instituted as soon as the patient's condition warrants surgical intervention. Rib resection drainage is particularly applicable in those cases in which the

empyema is uncomplicated and in those of empyema complicated by a rupture of the visceral pleura. Of far greater importance to the life of a patient with empyema is the management of the postpneumonic complications associated with the empyema. In these cases it must be re-emphasized that such complications are often of greater importance to the life of the patient than the empyema itself and that therefore efforts must be made to minimize the gravity of these complications before the empyema is attacked.

The number of deaths from empyema per se is not great as compared with the tremendous mortality from complicated empyema. In the 202 cases of uncomplicated empyema (80 streptococcic and 122 pneumococcic), there were seventeen mortalities (eleven streptococcic and six pneumococcic), a gross mortality of 8 per cent. In the eighty-three cases of complicated empyema (forty-four streptococcic and thirty-nine pneumococcic), there were fifty-eight mortalities (thirty-three streptococcic and twenty-five pneumococcic), a gross mortality of 70 per cent. In the uncomplicated thirty-one cases of empyema in children below 2 years of age, there were two deaths, a mortality of 6 per cent, whereas in the complicated twenty cases, there were seventeen deaths, a mortality of 85 per cent. It is of interest to note that the mortality in the uncomplicated empyemas in children below 2 years of age is even less than that for the general group of cases, whereas in the complicated cases, it is higher than in the other cases. Further, it must be added that while only 17 per cent of the total number of cases in this series were below 2 years of age, 24 per cent of the total number of complicated cases were in this age group. It appears, therefore, that complications tend to occur more frequently in children below the age of 2 years. This occurrence may be explained on the bases that older children and adults have acquired some degree of immunity to the common etiological organisms of pneumonia whereas the youngest subjects have not. If we consider pneumonia as a bacteriemia, as some do, with local expression in a susceptible organ (the lung), then we may postulate further that the increase in incidence of empyema in young children is due to poorer local tissue resistance or immunity. This explanation is in accord with the observations of Heuer[24] and Graham and Berck[25] who showed that at any given period the deaths from empyema correspond to the death rate for pneumonia and that both are apparently related to the virulence of the specific organism.

CONCLUSIONS

1. Empyema is rarely a surgical emergency, whereas its complications may be.

2. Complications associated with empyema occur more frequently in patients below 2 years of age than after that age.

3. The mortality in complicated empyema is almost ten times as great as it is in uncomplicated empyema.

4. The mortality from empyema is related, not to the age of the patient, but rather to the incidence and severity of the associated complications.

5. Aspiration should be reserved for diagnosis rather than for the treatment of empyema.

6. Intercostal drainage should be reserved for palliative treatment and for those cases in which the pus is thin.

7. Rib resection drainage should be instituted after the acute pneumonic process has subsided and the pus has become viscid.

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Notice to Members

The dates for the annual meeting are June 9, 10, and 11. The headquarters will be at The Royal York Hotel, Toronto. The manager is setting aside a large number of rooms for our use, and reservations should be made by writing directly to him. Dr. Robert M. Janes, 170 St. George Street, Toronto, Ontario, is Chairman of the Local Committee of Arrangements.

March 1 is the closing date for receiving applications for places on the program and also for the Rose Lampert Graff Prize. Members wishing to enter their papers for this prize must send the complete paper to the Secretary, without identifying marks but accompanied by a sealed envelope containing the name of the author. Contributions for the program which are not to be considered for the prize should consist of a comprehensive abstract of the paper as well as the title. Prompt submission of papers and applications will be very much appreciated by the Program Committee.

RICHARD H. MEADE, JR.
Secretary

Book Review

La Toracoplastia en el Tratamiento de la Tuberculosis Pulmonar. By Hernan D. Aguilar. Buenos Aires, 1938, El Ateneo, 2 volumes, pp. 1504.

This work is the most exhaustive treatise on the subject of thoracoplasty which has been published in any language up to this time. It includes two volumes comprising a total of 1504 pages. The author, Hernan D. Aguilar, is a pupil of the distinguished Argentine surgeon, Professor Ricardo Finochietto of the University of Buenos Aires. It provides a splendid opportunity, therefore, for us in the United States to become acquainted with the many original methods used by that resourceful surgeon, which culminate in his highly interesting muscle-splitting incision for thoracoplasty, an incision which makes it possible to perform the operation almost bloodlessly.

The book consists of ten parts. The first has two chapters containing a historical review of the surgical treatment of pulmonary tuberculosis, with a description of the evolution of thoracoplasty in South America, particularly in Argentina. The second part deals largely with the surgical anatomic features of thoracoplasty, with special emphasis on those which are involved in Finochietto's method without the cutting of muscles. Then there follows in Part 3 an extensive discussion of the anatomic and physiologic changes induced by surgical intervention in pulmonary tuberculosis, with emphasis on the processes involved in the healing of cavities and in the formation of scar tissue, the effect of thoracoplasty on the respiratory mechanism, etc. In Part 4 there is an excellent presentation of the indications for thoracoplasty. In the six chapters of 5 the author discusses in detail the questions of the choice of operation, with special consideration of incisions, the use of partial or total thoracoplasty, the choice of anesthesia, and other technical questions. There follows in Part 6 an extensive discussion of the possibilities of thoracoplasty used in conjunction with other forms of treatment of pulmonary tuberculosis, such as artificial pneumothorax, intrapleural and extrapleural pneumonolysis, elastic thoracoplasties, scaleniotomy, intercostal nerve resection, etc. Part 7 deals with the technical features of the operation of thoracoplasty, and Finochietto's operation is described in great detail. The concluding parts deal chiefly with the postoperative care, the complications, the effects of thoracoplasty on the spine, and finally, an analysis of the results.

The book is profusely illustrated with excellent line drawings, reproductions of x-ray films, and diagrams. There is a bibliography of 672 references and a very good index.

Although the work is written in Spanish, the illustrations are so well selected that there is no difficulty in understanding the main points, even on the part of one who is not adept in that language. This monumental work should be in the library of every thoracic surgeon. It is a pleasure to the reviewer to recommend to the English-speaking world this scholarly contribution to the subject from our friends in a distant part of America. The high standards of Argentine medicine, of course, have long been known to us in the United States. This work by Aguilar, however, again splendidly emphasizes the quality of those standards.

Evarts A. Graham.